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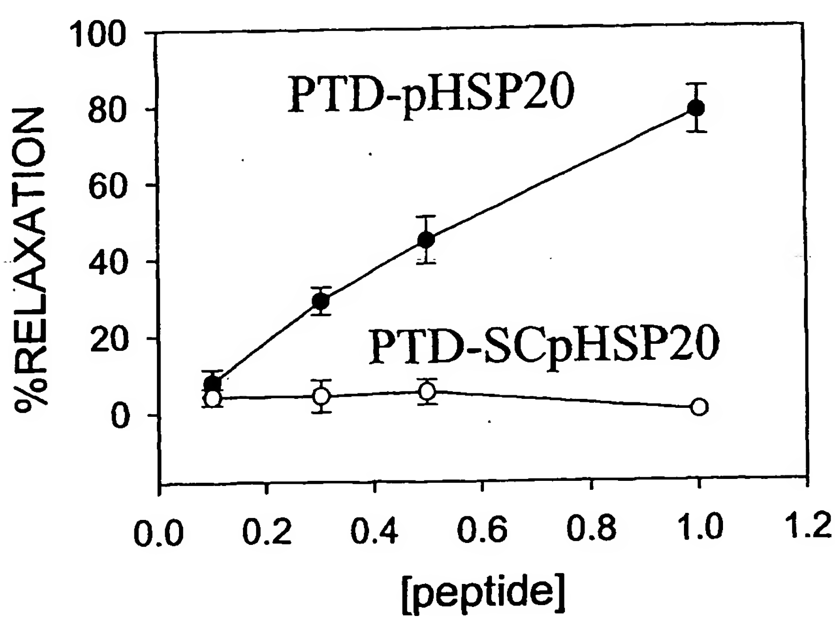
(54) Title: REAGENTS AND METHODS FOR SMOOTH MUSCLE THERAPIES



(57) Abstract: The present invention provides novel polypeptides comprising heat shock protein 20 (HSP20)-derived polypeptides to treat or inhibit smooth muscle vasospasm, as well to treat and inhibit smooth muscle cell proliferation and migration.

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REAGENTS AND METHODS FOR SMOOTH MUSCLE THERAPIES

CROSS REFERENCE

This application claims priority from U.S. Provisional Patent Application Serial No. 60/314,535 filed August 23, 2001, the disclosure of which is incorporated by reference herein in its entirety.

STATEMENT OF GOVERNMENT FUNDING

The U.S. Government through the National Institute of Health, provided financial assistance for this project under Grant No. RO1 HL58027-06. Therefore, the United States Government may own certain rights to this invention.

FIELD OF INVENTION

This invention relates generally to the fields of cell biology, molecular biology, pharmaceuticals, and smooth muscle biology.

BACKGROUND

There are three types of muscles: cardiac, skeletal, and smooth. Smooth muscles are found in the walls of blood vessels, airways, the gastrointestinal tract, and the genitourinary tract. The caliber of tubes lined by these muscles is dependent on a dynamic balance between the state of contraction and the state of relaxation of the muscles in these organs. Contraction and relaxation of smooth muscles are mediated by different signaling pathways inside the muscles. Pathways which induce relaxation also inhibit contraction. Sustained contraction of muscle is a "spasm" of the muscle. This spasm can be prevented by activating pathways or systems which induce relaxation, or in other words, inhibit contraction.

For the most part, smooth muscles are unique in that they lack the ordered structure of cardiac and skeletal muscles and that they are able to maintain tonic contractions with minimal oxygen use. Pathologic tonic contraction is a state in which the muscles are in spasm.

Many pathological conditions are associated with spasm of vascular smooth muscle ("vasospasm"), the smooth muscle that lines blood vessels. Vasospasm, of the

vessel causes narrowing of the vessel lumen, limiting blood flow. Spasm of any vessel leads to ischemia to the organ that the vessel supplies blood to. Ischemia is reversible lack of blood flow and oxygen supply to the tissues. In the case of spasm of the vessels in the heart it leads to cardiac ischemia and/or infarction; spasm of vessels in the brain leads to stroke; spasm of the vessels that supply the intestines leads to mesenteric ischemia, a lack of relaxation of the vessels in the penis leads to impotence, since erection requires vasodilation of the corpra cavernosal (penile) blood vessels; and spasm of the intracranial blood vessels leads to migraines.

Excessive vasoconstriction (or inadequate vasodilation) occur in other disease states as well. Hypertension (high blood pressure) is caused by excessive vasoconstriction, as well as thickening, of the vessel wall, particularly in the smaller vessels of the circulation. This process may affect the lung vessels as well and cause pulmonary (lung) hypertension and asthma (bronchospasm). Other disorders known to be associated with excessive constriction, or inadequate dilation of smooth muscles include toxemia of pregnancy, pre-term labor, pre-eclampsia/eclampsia, Raynaud's disease or phenomenon, anal fissure, achalasia, hemolytic-uremia, and Prinzmetal's angina, a form of coronary spasm that causes angina. Spasm in the coronary arteries also occurs during mechanical manipulation of coronary arteries, such as during angioplasty and stenting. This spasm can lead to ischemia and infarction.

Surgical procedures involving the vasculature are also complicated by vasospasm of smooth muscle, which may result in both short term and long term complications including restenosis and vascular occlusion. There is a general pattern in which vasospasm, if persistent, leads to constrictive remodeling/intimal hyperplasia, and ultimately vascular occlusion. Corrective surgical procedures, such as stenting of a blood vessel, angioplasty, and implanting prosthetic devices such as dialysis access fistulas and shunts, are accompanied by damage to the smooth muscle. This leads to smooth muscle cell proliferation and migration. This ultimately leads to constrictive remodeling and intimal hyperplasia. This process leads to restenosis, prosthetic graft failure, stent and stent graft failure, microvascular graft failure, atherosclerosis, and transplant vasculopathy.

While incompletely understood, intimal hyperplasia is mediated by a sequence of events that include endothelial cell injury and vascular smooth muscle proliferation and migration from the media to the intima. This is associated with a phenotypic modulation of the smooth muscle cells from a contractile to a synthetic phenotype.

The "synthetic" smooth muscle cells secrete extracellular matrix proteins, which leads to pathologic vascular occlusion, as described above. Furthermore, increased proliferation and migration of smooth muscle cells can also lead to smooth muscle cell tumors, such as leiomyosarcomas and leiomyomas.

Thus, it would be of great benefit to identify new methods and therapeutics to treat or inhibit smooth muscle vasospasm, promote smooth muscle relaxation, improve other therapies involving smooth muscle, and to treat and inhibit smooth muscle cell proliferation and migration.

Summary of the Invention

The present invention provides new methods and therapeutics to treat or inhibit smooth muscle vasospasm, promote smooth muscle relaxation, improve other therapies involving smooth muscle, and to treat and inhibit smooth muscle cell proliferation and migration.

In one aspect, the present invention provides polypeptides consisting of an amino acid sequence according to general formula I:

$$X1\text{-}X2\text{-}[X3\text{-}A(X4)APLP\text{-}X5\text{-}]_u\text{-}X6$$

wherein X1 is absent or is one or more molecules comprising one or more aromatic ring;

X2 is absent or comprises a transduction domain;

X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (**SEQ ID NO:1**);

X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,

wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S and T;

X6 is absent or comprises a transduction domain; and

wherein u is 1-5.

In a preferred embodiment, X4 is phosphorylated. In a further preferred embodiment, at least one of X2 and X6 comprises a transduction domain.

In another aspect, the invention provides polypeptides consisting of an amino acid sequence according to the general formula II:

$$X1\text{-}X2\text{-}[X3\text{-}A(X4)APLP\text{-}X5]_u\text{-}X6$$

wherein X1 is absent or is one or more molecules comprising one or more aromatic ring;

X2 is absent or comprises a cell transduction domain;

X3 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of **SEQ ID NO:297**;

X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

X5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160 of **SEQ ID NO:297**;

X6 is absent or comprises a cell transduction domain; and

wherein at least one of X2 and X6 comprise a transduction domain.

In a preferred embodiment, X4 is phosphorylated.

In another aspect, the present invention provides pharmaceutical compositions, comprising one or more polypeptides of the present invention and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides isolated nucleic acid sequences encoding a polypeptide of the present invention. In further aspects, the present invention provides recombinant expression vectors comprising the nucleic acid sequences of the present invention, and host cells transfected with the recombinant expression vectors of the present invention.

In another aspect, the invention provides improved biomedical devices, wherein the biomedical devices comprise one or more polypeptides of the present invention disposed on or in the biomedical device. In various embodiments, such biomedical devices include stents, grafts, shunts, stent grafts, angioplasty devices, balloon catheters, fistulas, and any implantable drug delivery device.

In another aspect, the invention provides methods for inhibiting smooth muscle cell proliferation and/or migration, comprising contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of one or more polypeptide of the present invention. In various preferred embodiments of this aspect of the invention, the method is used to treat or prevent a disorder selected from the group consisting of intimal hyperplasia, stenosis,

restenosis, and atherosclerosis. In various other preferred embodiments of this aspect of the invention, the method is performed on a subject who has undergone, is undergoing, or will undergo a procedure selected from the group consisting of angioplasty, vascular stent placement, endarterectomy, atherectomy, bypass surgery, vascular grafting, organ transplant, prosthetic implant, microvascular reconstructions, plastic surgical flap reconstruction, and catheter emplacement. In a further embodiment of this aspect of the invention, the method is used to treat smooth muscle cell tumors.

In a further aspect, the present invention comprises methods for treating or inhibiting a disorder selected from the group consisting of intimal hyperplasia, stenosis, restenosis, and/or atherosclerosis, comprising contacting a subject in need thereof with an amount effective to treat or inhibit intimal hyperplasia, stenosis, restenosis, and/or atherosclerosis of HSP20, or a functional equivalent thereof.

In a further aspect, the present invention comprises methods for treating smooth muscle cell tumors comprising contacting a subject in need thereof with an amount effective to treat smooth muscle tumors of HSP20, or a functional equivalent thereof.

In a further aspect, the present invention provides a method for treating or preventing smooth muscle spasm, comprising contacting a subject in need thereof with an amount effective to inhibit smooth muscle spasm of one or more polypeptides of the present invention. In various preferred embodiments of this aspect of the invention, the muscle cell spasm is associated with a disorder or condition selected from the group consisting of angina, Prinzmetal's angina (coronary vasospasm), ischemia, stroke, bradycardia, hypertension, pulmonary (lung) hypertension, asthma (bronchospasm), toxemia of pregnancy, pre-term labor, pre-eclampsia/eclampsia, Raynaud's disease or phenomenon, hemolytic-uremia, non-occlusive mesenteric ischemia, anal fissure, achalasia, impotence, migraine, ischemic muscle injury associated with smooth muscle spasm, and vasculopathy, such as transplant vasculopathy.

In a further aspect, the present invention provides methods for promoting smooth muscle relaxation, comprising contacting smooth muscle with an amount effect effective to promote smooth muscle relaxation with one or more of the polypeptide of the present invention.

Brief Description of the Figures

Figure 1. Mesangial cells were transfected with vectors containing green fluorescent protein (GFP) alone, GFP fused to the 5' end of the wild type cDNA for HSP20 (WT), or GFP fused to an HSP20 construct in which the PKA phosphorylation site was mutated to an alanine (S16A-HSP20)(MUT) and the number of wrinkles under the cells was determined after treatment with dibutyryl cAMP (10 μM) for 0 minutes, 30 minutes, 60 minutes, or 90 minutes.

Figure 2. Mesangial cells were transduced with FITC-TAT-HSP20 and the number of wrinkles under the cells was determined at the time points indicated using phase contrast microscopy ($n = 10$, * = $p < 0.05$ compared to time 0).

Figure 3. Transverse strips of bovine carotid artery smooth muscle, denuded of endothelium, were pre-contracted with serotonin (1 μM for 10 minutes), cumulative doses of FITC-phospho-HSP20-TAT, FITC-scrambled phosphoHSP20-TAT (FITC-NH_2-βAGGGGYGRKKRRQRRRPRKS*LWALGRPLA-COOH, open circles) (**SEQ ID NO:305**), or FITC-TAT (FITC- NH_2-βAGGGGYGRKKRRQRRR, closed triangles) (**SEQ ID NO:306**) were added every 10 minutes, and the percent contraction was calculated. The force is depicted as a percentage of the maximal serotonin contraction ($n = 5$, * = $p < 0.05$ compared to 0 peptide added).

Figure 4. Rings of porcine coronary artery in which the endothelium was **not** denuded, were pre-contracted with serotonin (1 μM for 10 minutes), cumulative doses of PTD-pHSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH, closed circles) (**SEQ ID NO:307**) or PTD-scrambled-pHSP20 (NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH open circles) (**SEQ ID NO:308**) were added every 10 minutes, and the percentage of relaxation was calculated as a percentage of the maximal serotonin contraction ($n = 5$, * = $p < 0.05$ compared to 0 peptide added). The concentrations of peptide used are depicted on the x axis.

Figure 5. Homogenates of mesangial cells (lane 1), rat aortic smooth muscle cells (lane 2), and PKG transfected rat aortic smooth muscle cells (lane 3) were immunoblotted for PKG (panel A) or HSP20 (panel B). In a separate experiment, mesangial cells were untreated (panel C) or treated with dibutyryl cAMP (10 μM, 15 minutes, panel D). The proteins were separated by 2-dimensional electrophoresis, transferred to immobilon and probed with anti-HSP20 antibodies. Increases in the

phosphorylation of HSP20 leads to a shift in the electrophoretic mobility of the protein to a more acidic isoform (arrow).

Figure 6. Transfected mesangial cells were fixed, and the actin filaments were stained with fluorescent-labeled phalloidin. Mesangial cells were transfected with EGFP alone (EGFP), S16A-HSP20 (MUT-EGFP), or wild type HSP20 (WT-EGFP). The cells were plated on a glass slides, and not treated (CONT) or treated with dibutyryl cAMP (10 μM, for 30 minutes, db-cAMP). The cells were fixed and stained with rhodamine phalloidin. Dibutyryl cAMP led to a loss of central actin stress fibers in EGFP but not S16A-HSP20 cells. In the cells overexpressing HSP20 the actin fibers were peripherally localized.

Figure 7. Bovine aortic endothelial cells were plated on glass coverslips (80K-100K cells) in DMEM plus 10 % FBS over night (24 wells plate). The cells were serum starved (no serum) for one hour and incubated in the presence of the peptide analogues of HSP20 [NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH - pHSP20 (10 uM) **(SEQ ID NO:307)** or scrambled analogues of HSP20 [NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH -scHSP20 (10 uM)] **(SEQ ID NO:308)** for 30 minutes. The cells were fixed with 3% glutaraldehyde and the number of focal adhesions was detected with interference reflection microscopy. The Hep I peptide was used as a positive control.

Figure 8. Confluent A10 cells were serum starved (0.5% fetal bovine serum, FBS) for 48 hours. A linear wound was made in the smooth muscle cell monolayer using a rubber scraper and the scratched edges were marked using metal pins. The cells were changed to 10% FBS media containing PTD-pHSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH **(SEQ ID NO:307)**, or PTD-scrambled-pHSP20 (NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH **(SEQ ID NO:308)** (50 μM) and incubated for 24 hours. The cells were fixed and stained with hematoxylin. The number of cells migrating into a 1 cm^2 scratched area were counted as an index for migration. In additional experiments, the migration of A10 cells was determined in a Boyden chamber assay.

Figure 9. A10 cells were serum starved for 3 days. The cells were then treated with media containing 10% fetal bovine serum, PTD-pHSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH **(SEQ ID NO:307)**, or PTD-

scrambled-pHSP20 (NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH **(SEQ ID NO:308)** (50 μM). After 24 hours cell counts were performed.

Detailed Description of the Invention

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutshcer, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), and *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.)

In one aspect, the present invention provides polypeptides consisting of an amino acid sequence according to general formula I:

X1-X2-[X3-A(X4)APLP-X5-]$_u$-X6

wherein X1 is absent or is one or more molecules comprising one or more aromatic ring;

X2 is absent or comprises a transduction domain;

X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR **(SEQ ID NO:1)**;

X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

X5 is 0, 1, 2,or 3 amino acids of a sequence of genus Z1-Z2-Z3,

wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S and T;

X6 is absent or comprises a transduction domain; and

wherein u is 1-5.

Both single letter and three letter amino acid abbreviations are used within the application. As used herein, "norL" means norleucine and "Orn" means ornithine.

The term "polypeptide" is used in its broadest sense to refer to a sequence of subunit amino acids, amino acid analogs, or peptidomimetics. The subunits are linked by peptide bonds, except where noted (including when the X2 position is a non-amino acid molecule that contains an aromatic ring). The polypeptides described herein may be chemically synthesized or recombinantly expressed.

Preferably, the polypeptides of the present invention are chemically synthesized. Synthetic polypeptides, prepared using the well known techniques of solid phase, liquid phase, or peptide condensation techniques, or any combination thereof, can include natural and unnatural amino acids. Amino acids used for peptide synthesis may be standard Boc (Na-amino protected Na-t-butyloxycarbonyl) amino acid resin with the standard deprotecting, neutralization, coupling and wash protocols of the original solid phase procedure of Merrifield (1963, J. Am. Chem. Soc. 85:2149-2154), or the base-labile Na-amino protected 9-fluorenylmethoxycarbonyl (Fmoc) amino acids first described by Carpino and Han (1972, J. Org. Chem. 37:3403-3409). Both Fmoc and Boc Na-amino protected amino acids can be obtained from Sigma, Cambridge Research Biochemical, or other chemical companies familiar to those skilled in the art. In addition, the polypeptides can be synthesized with other Na-protecting groups that are familiar to those skilled in this art.

Solid phase peptide synthesis may be accomplished by techniques familiar to those in the art and provided, for example, in Stewart and Young, 1984, Solid Phase Synthesis, Second Edition, Pierce Chemical Co., Rockford, Ill.; Fields and Noble, 1990, Int. J. Pept. Protein Res. 35:161-214, or using automated synthesizers. The polypeptides of the invention may comprise D-amino acids (which are resistant to L-amino acid-specific proteases in vivo), a combination of D- and L-amino acids, and various "designer" amino acids (e.g., ß-methyl amino acids, Ca-methyl amino acids, and Na-methyl amino acids, etc.) to convey special properties. Synthetic amino acids include ornithine for lysine, and norleucine for leucine or isoleucine.

In addition, the polypeptides can have peptidomimetic bonds, such as ester bonds, to prepare peptides with novel properties. For example, a peptide may be generated that incorporates a reduced peptide bond, i.e., R_1-CH_2-NH-R_2, where R_1 and R_2 are amino acid residues or sequences. A reduced peptide bond may be introduced as a dipeptide subunit. Such a polypeptide would be resistant to protease activity, and would possess an extended half-live in vivo.

According to various embodiments of the polypeptides of general formula I, the region $[X3\text{-}A(X4)APLP\text{-}X5\text{-}]_u$ may be present in 1, 2, 3, 4, or 5 copies. In a preferred embodiment, it is present in 1 copy. In other embodiments, it is present in multiple copies to provide increased efficacy for use of the polypeptides for inhibiting one or more of smooth muscle cell proliferation, smooth muscle cell migration, and smooth muscle spasm, and/or also for promoting smooth muscle vasorelaxation.

According to various embodiments of the polypeptides of general formula I, X4 is S, T, Y, D E, a phosphoserine mimic, or a phosphotyrosine mimic. It is more preferred that X4 is S, T, or Y; more preferred that X4 is S or T, and most preferred that X4 is S. In these embodiments where X4 is S, T, or Y, it is most preferred that X4 is phosphorylated. When X4 is D or E, these residues have a negative charge that mimics the phosphorylated state. The polypeptides of the invention are optimally effective in the methods of the invention when X4 is phosphorylated, is a phosphoserine or phosphotyrosine mimic, or is another mimic of a phosphorylated amino acid residue, such as a D or E residue. Examples of phosphoserine mimics include, but are not limited to, sulfoserine, amino acid mimics containing a methylene substitution for the phosphate oxygen, 4-phosphono(difluoromethyl)phenylanaline, and L-2-amino-4-(phosphono)-4,4-difuorobutanoic acid. Other phosphoserine mimics can be made by those of skill in the art; for example, see Otaka et al., Tetrahedron Letters 36:927-930 (1995). Examples of phosphotyrosine mimics include, but are not limited to, phosphonomethylphenylalanine, difluorophosphonomethylphenylalanine, fluoro-O-malonyltyrosine and O-malonyltyrosine. (See, for example, Akamatsu et. al., Bioorg Med Chem 1997 Jan;5(1):157-63).

In another preferred embodiment, X1 is one or more molecules comprising an aromatic ring. In one preferred embodiment, the one or molecules comprising an aromatic ring are amino acids, and X1 is $(F/Y/W)_z$, wherein "z" is 1-5 amino acids. Thus, for example, X1 can be 1 or 2 amino acid residues of any combination of F, Y, and W, such as F, FF, Y, YY, W, WW, FY, FW, YF, YW, WY, and WF. Alternatively, X1 can be a 3, 4, or 5 amino acid combination of F, Y, and W. In another preferred embodiment, the molecule comprising an aromatic ring is selected from the group of molecules comprising one or more aromatic rings which can optionally be substituted with halogen, lower alkyl, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, and heteroaryl. In a most preferred embodiment, the one or

more molecule comprising one or more aromatic ring comprise 9-fluorenylmethyl (Fm). Examples of such molecules include, but are not limited to 9-fluorenylmethylcarbonyl, 9-fluorenylmethylcarbamates, 9-fluorenylmethylcarbonates, 9-fluorenylmethyl esters, 9-fluorenylmethylphosphates, and S-9-fluorenylmethyl thioethers. In embodiments wherein the molecule comprising an aromatic ring is not an amino acid, it can be attached to the polypeptide by methods known in the art, including but not limited to, standard Fmoc protection chemistry employed in peptide synthesis.

According to various embodiments of the polypeptides of general formula I, X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1). If X3 consists of only one amino acid of the sequence, an "R" is present, since it is the carboxy-terminal amino acid of the sequence and it would be present at the amino terminus of the rest of the A(X4)APLP (SEQ ID NO: 2) sequence. If X3 consists of two amino acids of WLRR (SEQ ID NO:1), then the two amino acids added will be "RR". Other variations will be apparent to one of skill in the art based on the teachings herein.

Similarly, variations in the residues that can make up X5 will be apparent to one of skill in the art based on the teachings herein.

Thus, according to these various aspects, a representative sample of polypeptides according to general formula I include, but are not limited to the following: $(ASAPLP)_u$ (SEQ ID NO:3); $(ATAPLP)_u$ (SEQ ID NO:4); $(RASAPLP)_u$ (SEQ ID NO:5); $(RATAPLP)_u$ (SEQ ID NO:6); $(AYAPLP)_u$ (SEQ ID NO:7); $(RAYAPLP)_u$ (SEQ ID NO:8);$(RRASAPLP)_u$ (SEQ ID NO:9); $(LRRASAPLP)_u$ (SEQ ID NO:10); $(WLRRASAPLP)_u$; (SEQ ID NO:11) $(RRATAPLP)_u$ (SEQ ID NO:12); $(LRRATAPLP)_u$ (SEQ ID NO:13); $(WLRRATAPLP)_u$ (SEQ ID NO:14); $(RRAYAPLP)_u$ (SEQ ID NO:15); $(LRRAYAPLP)_u$ (SEQ ID NO:16); $(WLRRAYAPLP)_u$ (SEQ ID NO:17); $(RRASAPLPG)_u$ (SEQ ID NO:18); $(RRASAPLPD)_u$ (SEQ ID NO:19); $(RRASAPLPGL)_u$ (SEQ ID NO:20); $(RRASAPLPGK)_u$ (SEQ ID NO:21); $(RRASAPLPDL)_u$ (SEQ ID NO:22); $(RRASAPLPDK)_u$ (SEQ ID NO:23); $(RRASAPLPGLS)_u$ (SEQ ID NO:24); $(RRASAPLPGLT)_u$ (SEQ ID NO:25); $(RRASAPLPGKS)_u$ (SEQ ID NO:26); $(RRASAPLPGKT)_u$ (SEQ ID NO:27); $(RRASAPLPDLS)_u$ (SEQ ID NO:28); $RRASAPLPDLT)_u$ (SEQ ID NO:29); $(RRASAPLPDKS)_u$ (SEQ ID NO:30); $(RRASAPLPDKT)_u$ (SEQ ID NO:31); $(LRRASAPLPG)_u$ (SEQ ID NO:32);

$(LRRASAPLPD)_u$ (SEQ ID NO:33); $(LRRASAPLPGL)_u$ (SEQ ID NO:34); $(LRRASAPLPGK)_u$ (SEQ ID NO:35); $(LRRASAPLPDL)_u$ (SEQ ID NO:36); $(LRRASAPLPDK)_u$ (SEQ ID NO:37); $(LRRASAPLPGLS)_u$ (SEQ ID NO:38); $(LRRASAPLPGLT)_u$ (SEQ ID NO:39); $(LRRASAPLPGKS)_u$ (SEQ ID NO:40); $(LRRASAPLPGKT)_u$ (SEQ ID NO:41); $(LRRASAPLPDLS)_u$ (SEQ ID NO:42); $(LRRASAPLPDLT)_u$ (SEQ ID NO:43); $(LRRASAPLPDKS)_u$ (SEQ ID NO:44); $(LRRASAPLPDKT)_u$ (SEQ ID NO:45); $(WLRRASAPLPG)_u$ (SEQ ID NO:46); $(WLRRASAPLPD)_u$ (SEQ ID NO:47); $(WLRRASAPLPGL)_u$ (SEQ ID NO:48); $(WLRRASAPLPGK)_u$ (SEQ ID NO:49); $(WLRRASAPLPDL)_u$ (SEQ ID NO:50); $(WLRRASAPLPDK)_u$ (SEQ ID NO:51); $(WLRRASAPLPGLS)_u$ (SEQ ID NO:52); $(WLRRASAPLPGLT)_u$ (SEQ ID NO:53); $(WLRRASAPLPGKS)_u$ (SEQ ID NO:54); $(WLRRASAPLPGKT)_u$ (SEQ ID NO:55); $(WLRRASAPLPDLS)_u$ (SEQ ID NO:56); $(WLRRASAPLPDLT)_u$ (SEQ ID NO:57); $(WLRRASAPLPDKS)_u$ (SEQ ID NO:58); $(WLRRASAPLPDKT)_u$ (SEQ ID NO:59); $(RRATAPLPG)_u$ (SEQ ID NO:60); $(RRATAPLPD)_u$ (SEQ ID NO:61); $(RRATAPLPGL)_u$ (SEQ ID NO:62); $(RRATAPLPGK)_u$ (SEQ ID NO:63); $(RRATAPLPDL)_u$ (SEQ ID NO:64); $(RRATAPLPDK)_u$ (SEQ ID NO:65); $(RRATAPLPGLS)_u$ (SEQ ID NO:66); $(RRATAPLPGLT)_u$ (SEQ ID NO:67); $(RRATAPLPGKS)_u$ (SEQ ID NO:68); $(RRATAPLPGKT)_u$ (SEQ ID NO:69); $(RRATAPLPDLS)_u$ (SEQ ID NO:70); $(RRATAPLPDLT)_u$ (SEQ ID NO:71); $(RRATAPLPDKS)_u$ (SEQ ID NO:72); $(RRATAPLPDKT)_u$ (SEQ ID NO:73); $(LRRATAPLPG)_u$ (SEQ ID NO:74); $(LRRATAPLPD)_u$ (SEQ ID NO:75); $(LRRATAPLPGL)_u$ (SEQ ID NO:76); $(LRRATAPLPGK)_u$ (SEQ ID NO:77); $(LRRATAPLPDL)_u$ (SEQ ID NO:78); $(LRRATAPLPDK)_u$ (SEQ ID NO:79); $(LRRATAPLPGLS)_u$ (SEQ ID NO:80); $(LRRATAPLPGLT)_u$ (SEQ ID NO:81); $(LRRATAPLPGKS)_u$ (SEQ ID NO:82); $(LRRATAPLPGKT)_u$ (SEQ ID NO:83); $(LRRATAPLPDLS)_u$ (SEQ ID NO:84); $(LRRATAPLPDLT)_u$ (SEQ ID NO:85); $(LRRATAPLPDKS)_u$ (SEQ ID NO:86); $(LRRATAPLPDKT)_u$ (SEQ ID NO:87); $(WLRRATAPLPG)_u$ (SEQ ID NO:88); $(WLRRATAPLPD)_u$ (SEQ ID NO:89); $(WLRRATAPLPGL)_u$ (SEQ ID NO:90); $(WLRRATAPLPGK)_u$ (SEQ ID NO:91); $(WLRRATAPLPDL)_u$ (SEQ ID NO:92); $(WLRRATAPLPDK)_u$ (SEQ ID NO:93); $(WLRRATAPLPGLS)_u$ (SEQ ID NO:94); $(WLRRATAPLPGLT)_u$ (SEQ ID NO:95); $(WLRRATAPLPGKS)_u$ (SEQ ID NO:96); $(WLRRATAPLPGKT)_u$ (SEQ ID NO:97); $(WLRRATAPLPDLS)_u$ (SEQ ID NO:98); $(WLRRATAPLPDLT)_u$ (SEQ ID NO:99); $(WLRRATAPLPDKS)_u$

(SEQ ID NO:100); (WLRRATAPLPDKT)$_u$ (SEQ ID NO:101); (RRAYAPLPG)$_u$ (SEQ ID NO:102); (RRAYAPLPD)$_u$ (SEQ ID NO:103); (RRAYAPLPGL)$_u$ (SEQ ID NO:104); (RRAYAPLPGK)$_u$ (SEQ ID NO:105); (RRAYAPLPDL)$_u$ (SEQ ID NO:106); (RRAYAPLPDK)$_u$ (SEQ ID NO:107); (RRAYAPLPGLS)$_u$ (SEQ ID NO:108); (RRAYAPLPGLT)$_u$ (SEQ ID NO:109); (RRAYAPLPGKS)$_u$ (SEQ ID NO:110; (RRAYAPLPGKT)$_u$ (SEQ ID NO:111); (RRAYAPLPDLS)$_u$ (SEQ ID NO:112); (RRAYAPLPDLT)$_u$ (SEQ ID NO:113); (RRAYAPLPDKS)$_u$ (SEQ ID NO:114); (RRAYAPLPDKT)$_u$ (SEQ ID NO:115); (LRRAYAPLPG)$_u$ (SEQ ID NO:116); (LRRAYAPLPD)$_u$ (SEQ ID NO:117); (LRRAYAPLPGL)$_u$ (SEQ ID NO:118); (LRRAYAPLPGK)$_u$ (SEQ ID NO:119); (LRRAYAPLPDL)$_u$ (SEQ ID NO:120); (LRRAYAPLPDK)$_u$ (SEQ ID NO:121); (LRRAYAPLPGLS)$_u$ (SEQ ID NO:122); (LRRAYAPLPGLT)$_u$ (SEQ ID NO:123); (LRRAYAPLPGKS)$_u$ (SEQ ID NO:124); (LRRAYAPLPGKT)$_u$ (SEQ ID NO:125); (LRRAYAPLPDLS)$_u$ (SEQ ID NO:126); (LRRAYAPLPDLT)$_u$ (SEQ ID NO:127); (LRRAYAPLPDKS)$_u$ (SEQ ID NO:128); (LRRAYAPLPDKT)$_u$ (SEQ ID NO:129); (WLRRAYAPLPG)$_u$ (SEQ ID NO:130); (WLRRAYAPLPD)$_u$ (SEQ ID NO:131); (WLRRAYAPLPGL)$_u$ (SEQ ID NO:132); (WLRRAYAPLPGK)$_u$ (SEQ ID NO:133); (WLRRAYAPLPDL)$_u$ (SEQ ID NO:134); (WLRRAYAPLPDK)$_u$ (SEQ ID NO:135); (WLRRAYAPLPGLS)$_u$ (SEQ ID NO:136); (WLRRAYAPLPGLT)$_u$ (SEQ ID NO:137); (WLRRAYAPLPGKS)$_u$ (SEQ ID NO:138); (WLRRAYAPLPGKT)$_u$ (SEQ ID NO:139); (WLRRAYAPLPDLS)$_u$ (SEQ ID NO:140); (WLRRAYAPLPDLT)$_u$ (SEQ ID NO:141); (WLRRAYAPLPDKS)$_u$ (SEQ ID NO:142); and (WLRRAYAPLPDKT)$_u$ (SEQ ID NO:143); ((F/Y/W)RRASAPLP)$_u$ (SEQ ID NO:144); ((F/Y/W)LRRASAPLP)$_u$ (SEQ ID NO:145); ((F/Y/W)WLRRASAPLP)$_u$; (SEQ ID NO:146) ((F/Y/W)RRATAPLP)$_u$ (SEQ ID NO:147); ((F/Y/W)LRRATAPLP)$_u$ (SEQ ID NO:148); ((F/Y/W)WLRRATAPLP)$_u$ (SEQ ID NO:149); ((F/Y/W)RRAYAPLP)$_u$ (SEQ ID NO:150); ((F/Y/W)LRRAYAPLP)$_u$ (SEQ ID NO:151); ((F/Y/W)WLRRAYAPLP)$_u$ (SEQ ID NO:152); ((F/Y/W)RRASAPLPG)$_u$ (SEQ ID NO:153); ((F/Y/W)RRASAPLPD)$_u$ (SEQ ID NO:154); ((F/Y/W)RRASAPLPGL)$_u$ (SEQ ID NO:155); ((F/Y/W)RRASAPLPGK)$_u$ (SEQ ID NO:156); ((F/Y/W)RRASAPLPDL)$_u$ (SEQ ID NO:157); ((F/Y/W)RRASAPLPDK)$_u$ (SEQ ID NO:158); ((F/Y/W)RRASAPLPGLS)$_u$ (SEQ ID NO:159); ((F/Y/W)RRASAPLPGLT)$_u$ (SEQ ID NO:160); ((F/Y/W)RRASAPLPGKS)$_u$; (SEQ ID NO:161); ((F/Y/W)RRASAPLPGKT)$_u$ (SEQ

ID NO:162); ((F/Y/W)RRASAPLPDLS)$_u$ (SEQ ID NO:163); ((F/Y/W)RRASAPLPDLT)$_u$ (SEQ ID NO:164); ((F/Y/W)RRASAPLPDKS)$_u$ (SEQ ID NO:165); ((F/Y/W)RRASAPLPDKT)$_u$ (SEQ ID NO:166); ((F/Y/W)LRRASAPLPG)$_u$ (SEQ ID NO:167); ((F/Y/W)LRRASAPLPD)$_u$ (SEQ ID NO:168); ((F/Y/W))LRRASAPLPGL)$_u$ (SEQ ID NO:169); ((F/Y/W)LRRASAPLPGK)$_u$ (SEQ ID NO:170); ((F/Y/W)LRRASAPLPDL)$_u$ (SEQ ID NO:171); ((F/Y/W)LRRASAPLPDK)$_u$ (SEQ ID NO:172); ((F/Y/W)LRRASAPLPGLS)$_u$ (SEQ ID NO:173); ((F/Y/W)LRRASAPLPGLT)$_u$ (SEQ ID NO:174); ((F/Y/W)LRRASAPLPGKS)$_u$ (SEQ ID NO:175); ((F/Y/W)LRRASAPLPGKT)$_u$ (SEQ ID NO:176); ((F/Y/W)LRRASAPLPDLS)$_u$ (SEQ ID NO:177); ((F/Y/W)LRRASAPLPDLT)$_u$ (SEQ ID NO:178); ((F/Y/W)LRRASAPLPDKS)$_u$ (SEQ ID NO:179); ((F/Y/W)LRRASAPLPDKT)$_u$ (SEQ ID NO:180); ((F/Y/W)WLRRASAPLPG)$_u$ (SEQ ID NO:181); ((F/Y/W)WLRRASAPLPD)$_u$ (SEQ ID NO:182); ((F/Y/W)WLRRASAPLPGL)$_u$ (SEQ ID NO:183); ((F/Y/W)WLRRASAPLPGK)$_u$ (SEQ ID NO:184); ((F/Y/W)WLRRASAPLPDL)$_u$ (SEQ ID NO:185); ((F/Y/W)WLRRASAPLPDK)$_u$ (SEQ ID NO:186); ((F/Y/W)WLRRASAPLPGLS)$_u$ (SEQ ID NO:187); ((F/Y/W)WLRRASAPLPGLT)$_u$ (SEQ ID NO:188); ((F/Y/W)WLRRASAPLPGKS)$_u$ (SEQ ID NO:189); ((F/Y/W)WLRRASAPLPGKT)$_u$ (SEQ ID NO:190); ((F/Y/W)WLRRASAPLPDLS)$_u$ (SEQ ID NO:191); ((F/Y/W)WLRRASAPLPDLT)$_u$ (SEQ ID NO:192); ((F/Y/W)WLRRASAPLPDKS)$_u$ (SEQ ID NO:193); ((F/Y/W)WLRRASAPLPDKT)$_u$ (SEQ ID NO:194); ((F/Y/W)RRATAPLPG)$_u$ (SEQ ID NO:195); ((F/Y/W)RRATAPLPD)$_u$ (SEQ ID NO:196); ((F/Y/W)RRATAPLPGL)$_u$ (SEQ ID NO:197); ((F/Y/W)RRATAPLPGK)$_u$ (SEQ ID NO:198); ((F/Y/W)RRATAPLPDL)$_u$ (SEQ ID NO:199); ((F/Y/W)RRATAPLPDK)$_u$ (SEQ ID NO:200); ((F/Y/W)RRATAPLPGLS)$_u$ (SEQ ID NO:201); ((F/Y/W)RRATAPLPGLT)$_u$ (SEQ ID NO:202); ((F/Y/W)RRATAPLPGKS)$_u$ (SEQ ID NO:203); ((F/Y/W)RRATAPLPGKT)$_u$ (SEQ ID NO:204); ((F/Y/W)RRATAPLPDLS)$_u$ (SEQ ID NO:205); ((F/Y/W)RRATAPLPDLT)$_u$ (SEQ ID NO:206); ((F/Y/W)RRATAPLPDKS)$_u$ (SEQ ID NO:207); ((F/Y/W)RRATAPLPDKT)$_u$ (SEQ ID NO:208); ((F/Y/W)LRRATAPLPG)$_u$ (SEQ ID NO:209); ((F/Y/W)LRRATAPLPD)$_u$ (SEQ ID NO:210); ((F/Y/W)LRRATAPLPGL)$_u$ (SEQ ID NO:211); ((F/Y/W)LRRATAPLPGK)$_u$ (SEQ ID NO:212); ((F/Y/W)LRRATAPLPDL)$_u$ (SEQ ID NO:213);

$((F/Y/W)LRRATAPLPDK)_u$ (SEQ ID NO:214); $((F/Y/W)LRRATAPLPGLS)_u$ (SEQ ID NO:215); $((F/Y/W)LRRATAPLPGLT)_u$ (SEQ ID NO:216); $((F/Y/W)LRRATAPLPGKS)_u$ (SEQ ID NO:217); $((F/Y/W)LRRATAPLPGKT)_u$ (SEQ ID NO:218); $((F/Y/W)LRRATAPLPDLS)_u$ (SEQ ID NO:219); $((F/Y/W)LRRATAPLPDLT)_u$ (SEQ ID NO:220); $((F/Y/W)LRRATAPLPDKS)_u$ (SEQ ID NO:221); $((F/Y/W)LRRATAPLPDKT)_u$ (SEQ ID NO:222); $((F/Y/W)WLRRATAPLPG)_u$ (SEQ ID NO:223); $((F/Y/W)WLRRATAPLPD)_u$ (SEQ ID NO:224); $((F/Y/W)WLRRATAPLPGL)_u$ (SEQ ID NO:225); $((F/Y/W)WLRRATAPLPGK)_u$ (SEQ ID NO:226); $((F/Y/W)WLRRATAPLPDL)_u$ (SEQ ID NO:227); $((F/Y/W)WLRRATAPLPDK)_u$ (SEQ ID NO:228); $((F/Y/W)WLRRATAPLPGLS)_u$ (SEQ ID NO:229); $((F/Y/W)WLRRATAPLPGLT)_u$ (SEQ ID NO:230); $((F/Y/W)WLRRATAPLPGKS)_u$ (SEQ ID NO:231); $((F/Y/W)WLRRATAPLPGKT)_u$ (SEQ ID NO:232); $((F/Y/W)WLRRATAPLPDLS)_u$ (SEQ ID NO:233); $((F/Y/W)WLRRATAPLPDLT)_u$ (SEQ ID NO:234); $((F/Y/W)WLRRATAPLPDKS)_u$ (SEQ ID NO:235); $((F/Y/W)WLRRATAPLPDKT)_u$ (SEQ ID NO:236); $((F/Y/W)RRAYAPLPG)_u$ (SEQ ID NO:237); $((F/Y/W)RRAYAPLPD)_u$ (SEQ ID NO:238); $((F/Y/W)RRAYAPLPGL)_u$ (SEQ ID NO:239); $((F/Y/W)RRAYAPLPGK)_u$ (SEQ ID NO:240); $((F/Y/W)RRAYAPLPDL)_u$ (SEQ ID NO:241); $((F/Y/W)RRAYAPLPDK)_u$ (SEQ ID NO:242); $((F/Y/W)RRAYAPLPGLS)_u$ (SEQ ID NO:243); $((F/Y/W)RRAYAPLPGLT)_u$ (SEQ ID NO:244); $((F/Y/W)RRAYAPLPGKS)_u$ (SEQ ID NO:245); $((F/Y/W)RRAYAPLPGKT)_u$ (SEQ ID NO:246); $((F/Y/W)RRAYAPLPDLS)_u$ (SEQ ID NO:247); $((F/Y/W)RRAYAPLPDLT)_u$ (SEQ ID NO:248); $((F/Y/W)RRAYAPLPDKS)_u$ (SEQ ID NO:249); $((F/Y/W)RRAYAPLPDKT)_u$ (SEQ ID NO:250); $((F/Y/W)LRRAYAPLPG)_u$ (SEQ ID NO:251); $((F/Y/W)LRRAYAPLPD)_u$ (SEQ ID NO:252); $((F/Y/W)LRRAYAPLPGL)_u$ (SEQ ID NO:253); $((F/Y/W)LRRAYAPLPGK)_u$ (SEQ ID NO:254); $((F/Y/W)LRRAYAPLPDL)_u$ (SEQ ID NO:255); $((F/Y/W)LRRAYAPLPDK)_u$ (SEQ ID NO:256); $((F/Y/W)LRRAYAPLPGLS)_u$ (SEQ ID NO:257); $((F/Y/W)LRRAYAPLPGLT)_u$ (SEQ ID NO:258); $((F/Y/W)LRRAYAPLPGKS)_u$ (SEQ ID NO:259); $((F/Y/W)LRRAYAPLPGKT)_u$ (SEQ ID NO:260); $((F/Y/W)LRRAYAPLPDLS)_u$ (SEQ ID NO:261); $((F/Y/W)LRRAYAPLPDLT)_u$ (SEQ ID NO:262); $((F/Y/W)LRRAYAPLPDKS)_u$ (SEQ ID NO:263); $((F/Y/W)LRRAYAPLPDKT)_u$

(SEQ ID NO:264); ((F/Y/W)WLRRAYAPLPG)$_u$ (SEQ ID NO:265); ((F/Y/W)WLRRAYAPLPD)$_u$ (SEQ ID NO:266); ((F/Y/W)WLRRAYAPLPGL)$_u$ (SEQ ID NO:267); ((F/Y/W)WLRRAYAPLPGK)$_u$ (SEQ ID NO:268); ((F/Y/W)WLRRAYAPLPDL)$_u$ (SEQ ID NO:269); ((F/Y/W)WLRRAYAPLPDK)$_u$ (SEQ ID NO:270); ((F/Y/W)WLRRAYAPLPGLS)$_u$ (SEQ ID NO:271); ((F/Y/W)WLRRAYAPLPGLT)$_u$ (SEQ ID NO:272); ((F/Y/W)WLRRAYAPLPGKS)$_u$ (SEQ ID NO:273); ((F/Y/W)WLRRAYAPLPGKT)$_u$ (SEQ ID NO:274); ((F/Y/W)WLRRAYAPLPDLS)$_u$ (SEQ ID NO:275); ((F/Y/W)WLRRAYAPLPDLT)$_u$ (SEQ ID NO:276); ((F/Y/W)WLRRAYAPLPDKS)$_u$ (SEQ ID NO:277); and ((F/Y/W)WLRRAYAPLPDKT)$_u$ (SEQ ID NO:278) wherein "u" is as defined above, and (F/Y/W) means that the residue is selected from F, Y, and W. Other specific polypeptides falling within the scope of general formula I will be readily apparent to one of skill in the art based on the teachings herein.

In a further embodiment, the polypeptides of the present invention consist of a combination of different sequences from the region [X3-A(X4)APLP-X5-]$_u$. In this embodiment, for example, the polypeptide can consist of 1 copy of SEQ ID NO:9 and 1 copy of SEQ ID NO:143. In a different example, the polypeptide could consist of 2 copies of SEQID NO:200 and 3 copies of SEQ ID NO:62. It will be apparent to one of skill in the art that many such combinations are possible based on the teachings of the present invention.

In a preferred embodiment, at least one of X2 and X6 comprises a transduction domain. As used herein, the term "transduction domain" means one or more amino acid sequence or any other molecule that can carry the active domain across cell membranes. These domains can be linked to other polypeptides to direct movement of the linked polypeptide across cell membranes. In some cases the transducing molecules do not need to be covalently linked to the active polypeptide (for example, see sequence ID 291). In a preferred embodiment, the transduction domain is linked to the rest of the polypeptide via peptide bonding. (See, for example, *Cell* 55: 1179-1188, 1988; *Cell* 55: 1189-1193, 1988; *Proc Natl Acad Sci U S A* 91: 664-668, 1994; *Science* 285: 1569-1572, 1999; *J Biol Chem* 276: 3254-3261, 2001; and *Cancer Res* 61: 474-477, 2001) In this embodiment, any of the polypeptides as described above would include at least one transduction domain. In a further embodiment, both X2

and X6 comprise transduction domains. In a further preferred embodiment, the transduction domain(s) is/are selected from the group consisting of $(R)_{4-9}$ (SEQ ID NO:279); GRKKRRQRRRPPQ (SEQ ID NO:280); AYARAAARQARA (SEQ ID NO:281); DAATATRGRSAASRPTERPRAPARSASRPRRPVE (SEQ ID NO:282); GWTLNSAGYLLGLINLKALAALAKKIL (SEQ ID NO:283); PLSSIFSRIGDP (SEQ ID NO:284); AAVALLPAVLLALLAP (SEQ ID NO:285); AAVLLPVLLAAP (SEQ ID NO:286); VTVLALGALAGVGVG (SEQ ID NO:287); GALFLGWLGAAGSTMGAWSQP (SEQ ID NO:288); GWTLNSAGYLLGLINLKALAALAKKIL (SEQ ID NO:289); KLALKLALKALKAALKLA (SEQ ID NO:290); KETWWETWWTEWSQPKKKRKV (SEQ ID NO:291); KAFAKLAARLYRKAGC (SEQ ID NO:292); KAFAKLAARLYRAAGC (SEQ ID NO:293); AAFAKLAARLYRKAGC (SEQ ID NO:294); KAFAALAARLYRKAGC (SEQ ID NO:295); KAFAKLAAQLYRKAGC (SEQ ID NO:296), and AGGGGYGRKKRRQRRR (SEQ ID NO:306).

In another embodiment, the present invention provides a polypeptide comprising a sequence according to general formula II:

X1-X2-[X3-A(X4)APLP-X5]$_u$-X6

wherein X1 is absent or is one or more molecules comprising one or more aromatic ring;

X2 is absent or comprises a cell transduction domain;

X3 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of SEQ ID NO:297;

X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

X5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160 of SEQ ID NO:297;

X6 is absent or comprises a cell transduction domain; and

wherein at least one of X2 and X6 comprise a transduction domain.

Thus, in various preferred embodiments of the polypeptide of general formula II, X4 is S, T, Y, D, E, a phosphoserine analog, or a phosphotyrosine analog. In a

preferred embodiment, X4 is S, T, or Y. In a more preferred embodiment, X4 is S or T. In a most preferred embodiment, X4 is S.

In these embodiments where X4 is S, T, or Y, it is most preferred that X4 is phosphorylated. When X4 is D or E, these residues have a negative charge that mimics the phosphorylated state. The polypeptides of the invention are optimally effective in the methods of the invention when X4 is phosphorylated, is a phosphoserine or phosphotyrosine mimic, or is another mimic of a phosphorylated amino acid residue, such as a D or E residue.

In a further preferred embodiment, X1 is one or more molecules comprising one or more aromatic ring, as disclosed above, with preferred embodiments as disclosed above.

According to these embodiments, the polypeptide comprises at least one transduction domain. In a further embodiment, both X2 and X6 comprise a transduction domain. Preferred embodiments of such transduction domains are as described above.

One preferred embodiment of the polypeptide of general formula II comprises full length HSP20 (**X1-X2-SEQ ID NO:297-X6**).

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys. **(SEQ ID NO:297)**

Another preferred embodiment of the polypeptide of general formula II comprises full length HSP20 with the serine at position 16 substitute with aspartic acid (**X1-X2-SEQ ID NO:298-X6**):

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala **Asp** Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu

Leu Asp Val Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys. **(SEQ ID NO: 298)**

Another preferred embodiment of the polypeptide of general formula II comprises full length HSP20 with the serine at position 16 substitute with glutamic acid (X1-X2-**SEQ ID NO:299**-X6):

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala **Glu** Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys. **(SEQ ID NO: 299)**

Other preferred embodiments according to general formula II are the peptides disclosed above as embodiments of general formula I with the required transduction domain at either X2 or X6, or both. Still further preferred embodiments according to general formula II are the following:

X1-X2-**SEQ ID NO:300**-X6, wherein **(SEQ ID NO: 300)** is Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu Lys;

X1-X2-**SEQ ID NO:301**-X6, wherein **(SEQ ID NO: 301)** is Trp Leu Arg Arg Ala Asp Ala Pro Leu Pro Gly Leu Lys; and

X1-X2-**SEQ ID NO:302**-X6, wherein **(SEQ ID NO: 302)** is Trp Leu Arg Arg Ala Glu Ala Pro Leu Pro Gly Leu Lys.

In these embodiments of the polypeptides according to general formula II, it is preferred that the polypeptides are phosphorylated, most preferably at residue 16, or contain phosphorylation mimics at the position of amino acid residue 16.

In a further aspect, the present invention provides a composition, comprising one or more polypeptides of the present invention, and an inhibitor of HSP27. HSP27 is closely related to HSP20; the two proteins often co-exist in macromolecular

aggregates, and both are actin-associated proteins. Increases in the phosphorylation of HSP27 are associated with smooth muscle contraction, and transfection of cells with dominant active phosphorylated mutants of HSP27 leads to stress fiber formation (*Mol Cell Biol* 15: 505-516, 1995). Furthermore, increases in the phosphorylation of HSP27 are associated with smooth muscle cell migration. HSP20, in contrast, promotes vasorelaxation, and the data presented herein demonstrates that phosphorylated analogues of HSP20 lead to a loss of stress fiber formation, and inhibit smooth muscle cell proliferation and migration (See the examples below). Thus, the data indicate that HSP20 and HSP27 have opposing functions. Therefore, the combined use of one or more polypeptides of the invention and an inhibitor of HSP27 will have enhanced efficacy in carrying out the methods of the invention for inhibiting smooth muscle cell proliferation and/or migration, for promoting smooth muscle relaxation, and for inhibiting smooth muscle spasm (see below).

As used herein, an "inhibitor" of HSP27 includes HSP27 antibodies, anti-sense HSP27 nucleic acids, or small molecule inhibitors of the phosphorylation of HSP27, such as SB203580 (available from SmithKline Beecham).

The polypeptides may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

In another aspect, the present invention provides pharmaceutical compositions, comprising one or more of the polypeptides disclosed herein, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions are especially useful for carrying out the methods of the invention described below.

For administration, the polypeptides are ordinarily combined with one or more adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidine, dextran sulfate, heparin-containing gels, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration. Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may

include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The polypeptides or pharmaceutical compositions thereof may be administered by any suitable route, including orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intra-arterial, intramuscular, intrasternal, intratendinous, intraspinal, intracranial, intrathoracic, infusion techniques or intraperitoneally. Preferred embodiments for administration vary with respect to the condition being treated, and are described in detail below.

The polypeptides may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The polypeptides of the invention may be applied in a variety of solutions. Suitable solutions for use in accordance with the invention are sterile, dissolve sufficient amounts of the polypeptides, and are not harmful for the proposed application.

In another aspect, the present invention provides an isolated nucleic acid sequence encoding a polypeptide of the present invention. Appropriate nucleic acid sequences according to this aspect of the invention will be apparent to one of skill in the art based on the disclosure provided herein and the general level of skill in the art. One example of such a nucleic acid sequence is provided as **SEQ ID NO:320.**

In another aspect, the present invention provides an expression vector comprising DNA control sequences operably linked to the isolated nucleic acid molecules of the present invention, as disclosed above. "Control sequences" operably linked to the nucleic acid sequences of the invention are nucleic acid sequences capable of effecting the expression of the nucleic acid molecules. The control sequences need not be contiguous with the nucleic acid sequences, so long as they function to direct the expression thereof. Thus, for example, intervening untranslated yet transcribed sequences can be present between a promoter sequence and the nucleic acid sequences and the promoter sequence can still be considered "operably linked" to the coding sequence. Other such control sequences include, but are not limited to, polyadenylation signals, termination signals, and ribosome binding sites.

Such expression vectors can be of any type known in the art, including but not limited plasmid and viral-based expression vectors.

In a further aspect, the present invention provides genetically engineered host cells comprising the expression vectors of the invention. Such host cells can be prokaryotic cells or eukaryotic cells, and can be either transiently or stably transfected, or can be transduced with viral vectors.

In another aspect, the invention provides improved biomedical devices, wherein the biomedical devices comprise one or more of the polypeptides of the present invention disposed on or in the biomedical device. In a preferred embodiment, the one or more polypeptides are phosphorylated, as discussed above.

As used herein, a "biomedical device" refers to a device to be implanted into a subject, for example, a human being, in order to bring about a desired result. Particularly preferred biomedical devices according to this aspect of the invention include, but are not limited to, stents, grafts, shunts, stent grafts, fistulas, angioplasty devices, balloon catheters and any implantable drug delivery device.

As used herein, the term "grafts" refers to both natural and prosthetic grafts and implants. In a most preferred embodiment, the graft is a vascular graft.

As used herein, the term "stent" includes the stent itself, as well as any sleeve or other component that may be used to facilitate stent placement.

As used herein, "disposed on or in" means that the one or more polypeptides can be either directly or indirectly in contact with an outer surface, an inner surface, or embedded within the biomedical device. "Direct" contact refers to disposition of the polypeptides directly on or in the device, including but not limited to soaking a biomedical device in a solution containing the one or more polypeptides, spin coating or spraying a solution containing the one or more polypeptides onto the device, implanting any device that would deliver the polypeptide, and administering the polypeptide through a catheter directly on to the surface or into any organ.

"Indirect" contact means that the one or more polypeptides do not directly contact the biomedical device. For example, the one or more polypeptides may be disposed in a matrix, such as a gel matrix or a viscous fluid, which is disposed on the biomedical device. Such matrices can be prepared to, for example, modify the binding and release properties of the one or more polypeptides as required.

In a further embodiment, the biomedical device further comprises an inhibitor of the small heat shock protein HSP27 disposed on or in the biomedical device. In a preferred embodiment, such inhibitors are selected from HSP27 antibodies, anti-sense

HSP27 nucleic acids, or small molecule inhibitors of the phosphorylation of HSP27, such as SB203580.

In another aspect, the invention provides methods for inhibiting smooth muscle cell proliferation and/or migration, comprising contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of HSP20, or functional equivalents thereof, such as one or more polypeptide according to general formula I or II. In a most preferred embodiment, the one or more polypeptides are phosphorylated as disclosed above. In a further embodiment, the method further comprises contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of an inhibitor of the small heat shock protein HSP27. In a further embodiment, the method further comprises contacting the cells with an amount of PKG sufficient to stimulate HSP20 phosphorylation, wherein the contacting comprises transfecting the cells with an expression vector that is capable of directing the expression of PKG, or by transducing the cells with a PKG-transduction domain chimera.

Intimal hyperplasia is a complex process that leads to graft failure, and is the most common cause of failure of arterial bypass grafts. While incompletely understood, intimal hyperplasia is mediated by a sequence of events that include endothelial cell injury and subsequent vascular smooth muscle proliferation and migration from the media to the intima. This process is associated with a phenotypic modulation of the smooth muscle cells from a contractile to a synthetic phenotype. The "synthetic" smooth muscle cells secrete extracellular matrix proteins, which leads to pathologic narrowing of the vessel lumen leading to graft stenoses and ultimately graft failure. Such endothelial cell injury and subsequent smooth muscle cell proliferation and migration into the intima also characterizes restenosis, most commonly after angioplasty to clear an obstructed blood vessel. As discussed below, HSP20, and functional equivalents thereof, such as the polypeptides of general formula I and II, inhibit smooth muscle cell proliferation and migration.

In this aspect, the method can be in vitro or in vivo. In one embodiment, the method is in vitro, wherein a vein or arterial graft is contacted with HSP20 or a functional equivalent(s) thereof, prior to grafting in a patient, in order to inhibit smooth muscle cell proliferation and/or migration, and thus to inhibit subsequent intimal hyperplasia and stenosis after placement of the graft, which could lead to graft failure. This can be accomplished, for example, by delivering the recombinant

expression vectors (most preferably a viral vector, such as an adenoviral vector) of the invention to the site, and transfecting the smooth muscle cells. More preferably, delivery into smooth muscle cells is accomplished by using the polypeptides of general formula I or II that include at least one transduction domain to facilitate entry into the smooth muscle cells. The examples below demonstrate the ability of the polypeptides of the invention that contain at least one transduction domain to be delivered into smooth muscle cells.

In a more preferred in vitro embodiment, the method comprises contacting the graft with one or more of the polypeptides of the invention that include at least one transduction domain. Upon placement of the graft, it is preferred that the subject receiving be treated systemically with heparin, as heparin has been shown to bind to protein transduction domains and prevent them from transducing into cells. This approach will lead to localized protein transduction of the graft alone, and not into peripheral tissues.

In various other preferred embodiments of this aspect, the method is performed in vivo, and is used to treat or prevent a disorder selected from the group consisting of intimal hyperplasia, stenosis, restenosis, and atherosclerosis. In these embodiments, the contacting may be direct, by contacting a blood vessel in a subject being treated with HSP20 or a functional equivalent(s) thereof, such as the polypeptides according to general formula I or II. For example, a liquid preparation of HSP20 or a functional equivalent(s) thereof, such as the polypeptides according to general formula I or II, can be forced through a porous catheter, or otherwise injected through a catheter to the injured site, or a gel or viscous liquid containing the one or more polypeptides could be spread on the injured site. In these embodiment of direct delivery, it is most preferred that the HSP20 or a functional equivalent(s) thereof, such as the polypeptides according to general formula I or II be delivered into smooth muscle cells at the site of injury or intervention. This can be accomplished, for example, by delivering the recombinant expression vectors (most preferably a viral vector, such as an adenoviral vector) of the invention to the site. More preferably, delivery into smooth muscle cells is accomplished by using the polypeptides of general formula I or II that include at least one transduction domain to facilitate entry into the smooth muscle cells. The examples below demonstrate the ability of the polypeptides of the invention that contain at least one transduction domain to be delivered into smooth muscle cells.

In various other preferred embodiments of this aspect of the invention, the method is performed on a subject who has undergone, is undergoing, or will undergo a procedure selected from the group consisting of angioplasty, vascular stent placement, endarterectomy, atherectomy, bypass surgery (such as coronary artery bypass surgery; peripheral vascular bypass surgeries), vascular grafting, organ transplant, prosthetic device implanting, microvascular reconstructions, plastic surgical flap construction, and catheter emplacement.

In a further embodiment of this aspect of the invention, the method is used to treat smooth muscle cell tumors. In a preferred embodiment, the tumor is a leiomyosarcoma, which is defined as a malignant neoplasm that arises from muscle. Since leiomyosarcomas can arise from the walls of both small and large blood vessels, they can occur anywhere in the body, but peritoneal, uterine, and gastro-intestinal (particularly esophageal) leiomyosarcomas are more common. Alternatively, the smooth muscle tumor can be a leiomyoma, a non-malignant smooth muscle neoplasm. In a most preferred embodiment, the one or more polypeptides are phosphorylated as disclosed above. In a further embodiment, the method further comprises contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of an inhibitor of the small heat shock protein HSP27.

As further discussed in the examples below, HSP20, and functional equivalents thereof, such as the polypeptides of general formula I and II, also disrupt actin stress fiber formation and adhesion plaques, each of which have been implicated in intimal hyperplasia. The data further demonstrate a direct inhibitory effect of the polypeptides of the present invention on intimal hyperplasia. Thus, in another aspect, the present invention further provides methods for treating or inhibiting one or more disorder selected from the group consisting of intimal hyperplasia, stenosis, restenosis, and atherosclerosis, comprising contacting a subject in need thereof with an amount effective to treat or inhibit intimal hyperplasia, stenosis, restenosis, and/or atherosclerosis of HSP20, or a functional equivalent thereof, such as one or more polypeptides according to general formula I or II. Delivery of the HSP20, or a functional equivalent thereof, such as one or more polypeptides according to general formula I or II, in this aspect are as disclosed above. In a most preferred embodiment, the one or more polypeptides are phosphorylated as disclosed above. In a further embodiment, the method further comprises contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of an

inhibitor of the small heat shock protein HSP27.

In various other preferred embodiments of this aspect of the invention, the method is performed on a subject who has undergone, is undergoing, or will undergo a procedure selected from the group consisting of angioplasty, vascular stent placement, endarterectomy, atherectomy, bypass surgery, vascular grafting, microvascular reconstructions, plastic surgical flap construction, organ transplant, and catheter emplacement.

In a further aspect, the present invention provides methods to treat smooth muscle cell tumors, comprising administering to a subject in need thereof of an amount effective of HSP20, or a functional equivalent thereof, such as one or more polypeptides according to general formula I or II, to inhibit smooth muscle tumor growth and/or metastasis. In a preferred embodiment, the tumor is a leiomyosarcomas. Alternatively, the smooth muscle tumor can be a leiomyoma. In a further embodiment, the method further comprises contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of an inhibitor of the small heat shock protein HSP27.

In a further aspect, the present invention provides a method for treating or preventing smooth muscle spasm, comprising contacting a subject or graft in need thereof with an amount effective to inhibit smooth muscle spasm of HSP20, or a functional equivalent thereof, such as one or more polypeptides according to general formula I or II. In a most preferred embodiment, the one or more polypeptides are phosphorylated as disclosed above. In a further embodiment, the method further comprises contacting the smooth muscle with an amount effective to inhibit smooth muscle cell proliferation and/or migration of an inhibitor of the small heat shock protein HSP27. In a further embodiment, the method further comprises contacting the smooth muscle with an amount effective of PKG to stimulate HSP20 phosphorylation, as described above.

The examples below demonstrate that HSP20, and equivalents thereof, such as the polypeptides according to general formula I and II, are effective at inhibiting smooth muscle spasm, such as vasospasm. While not being limited by a specific mechanism of action, it is believed that HSP20, and equivalents thereof, such as the polypeptides according to general formula I and II, exert their anti-smooth muscle spasm effect by promoting smooth muscle vasorelaxation and inhibiting contraction.

Smooth muscles are found in the walls of blood vessels, airways, the gastrointestinal tract, and the genitourinary tract. Pathologic tonic contraction of smooth muscle constitutes spasm. Many pathological conditions are associated with spasm of vascular smooth muscle ("vasospasm"), the smooth muscle that lines blood vessels. This can cause symptoms such as angina and ischemia (if a heart artery is involved), or stroke as in the case of subarachnoid hemorrhage induced vasospasm if a brain vessel is involved. Hypertension (high blood pressure) is caused by excessive vasoconstriction, as well as thickening, of the vessel wall, particularly in the smaller vessels of the circulation.

Thus, in one embodiment of this aspect of the invention, the muscle cell spasm comprises a vasospasm, and the method is used to treat or inhibit vasospasm. Preferred embodiments of the method include, but are not limited to, methods to treat or inhibit angina, coronary vasospasm, Prinzmetal's angina (episodic focal spasm of an epicardial coronary artery), ischemia , stroke, bradycardia, and hypertension.

In another embodiment of this aspect of the invention, smooth muscle spasm is inhibited by treatment of a graft, such as a vein or arterial graft, with HSP20, or a functional equivalent thereof, such as one or more polypeptides according to general formula I or II, as described above. One of the ideal conduits for peripheral vascular and coronary reconstruction is the greater saphenous vein. However, the surgical manipulation during harvest of the conduit often leads to vasospasm. The exact etiology of vasospasm is complex and most likely multifactorial. Most investigations have suggested that vasospasm is either due to enhanced constriction or impaired relaxation of the vascular smooth muscle in the media of the vein. Numerous vasoconstricting agents such as endothelin-1 and thromboxane are increased during surgery and result in vascular smooth muscle contraction. Other vasoconstrictors such as norepinephrine, 5-hydroxytryptamine, acetylcholine, histamine, angiotensin II, and phenylephrine have been implicated in vein graft spasm. Papaverine is a smooth muscle vasodilator that has been used. In circumstances where spasm occurs even in the presence of papaverine, surgeons use intraluminal mechanical distension to break the spasm. This leads to injury to the vein graft wall and subsequent intimal hyperplasia. Intimal hyperplasia is the leading cause of graft failure.

Thus, in this embodiment, the graft can be contacted with HSP20 or a functional equivalent(s) thereof, during harvest from the graft donor, subsequent to harvest (before implantation), and/or during implantation into the graft recipient. This

can be accomplished, for example, by delivering the recombinant expression vectors (most preferably a viral vector, such as an adenoviral vector) of the invention to the site, and transfecting the smooth muscle cells. More preferably, delivery into smooth muscle is accomplished by using the polypeptides of general formula I or II that include at least one transduction domain to facilitate entry into the smooth muscle cells. The examples below demonstrate the ability of the polypeptides of the invention that contain at least one transduction domain to be delivered into smooth muscle cells. During graft implantation, it is preferred that the subject receiving be treated systemically with heparin, as heparin has been shown to bind to protein transduction domains and prevent them from transducing into cells. This approach will lead to localized protein transduction of the graft alone, and not into peripheral tissues. The methods of this embodiment of the invention inhibit vein graft spasm during harvest and/or implantation of the graft, and thus improve both short and long term graft success.

In various other embodiments, the muscle cell spasm is associated with a disorder including, but not limited to pulmonary (lung) hypertension, asthma (bronchospasm), toxemia of pregnancy, pre-term labor, pre-eclampsia/eclampsia, Raynaud's disease or phenomenon, hemolytic-uremia, non-occlusive mesenteric ischemia (ischemia of the intestines that is caused by inadequate blood flow to the intestines), anal fissure (which is caused by persistent spasm of the internal anal sphincter), achalasia (which is caused by persistent spasm of the lower esophageal sphincter), impotence (which is caused by a lack of relaxation of the vessels in the penis, erection requires vasodilation of the corpra cavernosal (penile) blood vessels), migraine (which is caused by spasm of the intracranial blood vessels), ischemic muscle injury associated with smooth muscle spasm, and vasculopathy, such as transplant vasculopathy (a reaction in the transplanted vessels which is similar to atherosclerosis, it involves constrictive remodeling and ultimately obliteration of the transplanted blood vessels, this is the leading cause of heart transplant failure).

Preferred routes of delivery for these various indications of the different aspects of the invention vary. Topical administration is preferred for methods involving treatment or inhibition of vein graft spasm, intimal hyperplasia, restenosis, prosthetic graft failure due to intimal hyperplasia, stent, stent graft failure due to intimal hyperplasia/constrictive remodeling, microvascular graft failure due to vasospasm, transplant vasculopathy, and male and female sexual dysfunction. As

used herein, "topical administration" refers to delivering the polypeptide onto the surface of the organ.

Intrathecal administration, defined as delivering the polypeptide into the cerebrospinal fluid is the preferred route of delivery for treating or inhibiting stroke and subarachnoid hemorrhage induced vasospasm. Intraperitoneal administration, defined as delivering the polypeptide into the peritoneal cavity, is the preferred route of delivery for treating or inhibiting non-occlusive mesenteric ischemia. Oral administration is the preferred route of delivery for treating or inhibiting achalasia. Intravenous administration is the preferred route of delivery for treating or inhibiting hypertension and bradycardia. Administration via suppository is preferred for treating or inhibiting anal fissure. Aerosol delivery is preferred for treating or inhibiting asthma (ie: bronchospasm). Intrauterine administration is preferred for treating or inhibiting pre-term labor and pre-eclampsia/eclampsia.

In practicing these various aspects of the invention, the amount or dosage range of the polypeptides or pharmaceutical compositions employed is one that effectively teats or inhibits one or more of smooth muscle cell proliferation, smooth muscle cell migration, smooth muscle spasm; and/or that promotes smooth muscle relaxation. Such an inhibiting (or promoting in the case of smooth muscle relaxation) amount of the polypeptides that can be employed ranges generally between about 0.01 μg/kg body weight and about 10 mg/kg body weight, preferably ranging between about 0.05 μg/kg and about 5 mg/kg body weight.

The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

EXAMPLES

Example 1

This Example illustrates a study of cyclic nucleotide-dependent phosphorylation of HSP20 in mesangial cells. The contractile phenotype and expression of PKG is lost as smooth muscle cells are passaged in culture. Mesangial cells have been shown to maintain a contractile phenotype in culture. To determine if mesangial cells in culture continue to express PKG and HSP20, multiply passaged

mesangial cells were compared to multiply passaged vascular smooth muscle cells and smooth muscle cells that had been stably transfected with PKG. The cells were homogenized and immunoblots were performed using rabbit polyclonal antibodies against PKG and HSP20. Multiply passaged vascular smooth muscle cells did not express PKG or HSP20. However, smooth muscle cells that had been stably transfected with PKG express PKG and HSP20. Cultured mesangial cells expressed similar amounts of both PKG and HSP20 as the PKG transfected vascular smooth muscle cells. These data suggest that the expression of PKG and the PKG substrate protein, HSP20, are coordinately regulated and that the expression of these proteins may be important for maintaining the cells in a contractile phenotype. Since phenotypic modulation from a contractile to a synthetic phenotype has been implicated in the response to injury model of atherogenesis and in the development of intimal hyperplasia, we propose that introducing HSP20 either via protein transduction or by gene transfection will provide a novel therapeutic approach to maintain cells in a contractile phenotype and prevent intimal hyperplasia.

Example 2

This Example illustrates the production of the HSP20 S16A mutant wherein the phosphorylation site (serine 16) was mutated to an alanine. The cDNA for HSP20 was cloned into pEGFP-C2 expression vector (commercially available from Clontech, Inc.) For production of the HSP20 S16A mutant, a single nucleotide mutation was introduced in the HSP20 cDNA sequence using a two complimentary oligonucleotide strategy with Pfu polumerase (commercially available from Stratagene, La Jolla, CA). All sequences were confirmed for orientation, the presence of the appropriate mutations, and the absence of other mutations, using a 377 Perkin-Elmer ABI Prism DNA sequencer (Foster City, CA). Similar techniques can be used to mutate the serine 16 for an aspartic or glutamic acid.

Example 3

This experiment illustrates that genetic manipulation of muscle like cells can alter their ability to contract. Specifically, engineering the cells to overexpress HSP20 prevents them from contracting (going into a state of spasm). If the cells overexpress a mutated form of HSP20 that cannot be phosphorylated, they remain contracted (in

spasm) even when treated with potent agents which cause relaxation. This experiment demonstrates that the phosphorylation of HSP20 is the seminal event required for muscles to relax.

The experiment was performed in the following fashion: Mesangial cells were transfected with vectors containing green fluorescent protein (GFP) alone, GFP fused to the 5' end of the wild type cDNA for HSP20 (WT), or GFP fused to an HSP20 construct in which the PKA phosphorylation site was mutated to an alanine (S16A-HSP20) (MUT). The cells were plated on a silicone rubber substrata in the presence of serum for 48 hours. The plates were then placed on the stage of a Zeiss Inverted Fluorescence Microscope with DeltaVision image acquisition and deconvolution software (Applied Precision, Issaquah, WA). The DeltaVision software was configured to eight different cells (x and y axis) on each plate with 7 z-axis images taken at 2 nm intervals. Fluorescent and phase contrast images were obtained such that the cells and silicone membrane were imaged in close succession. During the scanning process, the z-axis of each cell was monitored to assure that the imaging stacks were maintained at the appropriate level as the cells relaxed on the silicone membrane. Baseline images were acquired for one hour. The cells were then treated with the cells were treated with dibutyryl cAMP (10 μM) for 0 minutes, 30 minutes, 60 minutes, or 90 minutes, and the results are illustrated in **Figure 1**.

The control cells expressing the green fluorescent protein (GFP) in which the HSP20 was not changed relaxed over time (the wrinkles under the cells disappeared) when treated with dibutyryl cAMP. The cells over expressing HSP20 tagged to GFP (WT) did not form wrinkles; they were unable to contract or go into spasm. The cells expressing the mutated form of HSP20 that could not be phosphorylated (S16A-HSP20) (MUT) formed abundant wrinkles (contracted) but did not relax (remained in spasm) in response to dibutyryl cAMP. This figure is representative of 6 separate transfections in which at least 12 cells were imaged with each construct and the aggregate data is illustrated graphically (* = $p < 0.05$ compared to the initial number of wrinkles). Similar findings were observed when cyclic nucleotide-dependent signaling pathways were activated with sodium nitroprusside (10 μM), dibutyryl cGMP (10 μM), or forskolin (10 μM) (data not shown). There were no changes in the wrinkles in the substrata in untreated cells imaged for 90 minutes (data not shown). These data demonstrate that over expression of wild type HSP20 inhibits contraction

of the cells and expression of the S16A-HSP20 mutated protein inhibits relaxation. Thus, these data show that the phosphorylation of HSP20 is necessary and sufficient for the relaxation of smooth muscles, and suggests that phosphorylation of HSP20 represents a point in which the cyclic nucleotide signaling pathways converge to prevent contraction or cause relaxation.

Example 4

This experiment demonstrates that transduction of peptide analogues of phosphorylated HSP20 relaxes muscle-like cells. Phosphopeptide analogues of HSP20 were synthesized containing the TAT sequence (NH_2-βAGGGGYGRKKRRQRRRWLRRAS*APLPGLK-COOH) (referred to as FITC-TAT-HSP20) **(SEQ ID NO:304)** (the asterisk indicates that the "S"residue is phosphorylated). Mesangial cells were plated on a silicone substrata in the presence of serum and after 48 hours the cells were treated with the FITC-TAT-HSP20 phosphopeptide (50 μM). The number of wrinkles under the cells was determined at the time points indicated using phase contrast microscopy ($n = 10$, $* = p < 0.05$ compared to time 0). Results of this Experiment are illustrated in **Figure 2.** Treatment of the cells with the phosphopeptide analogue of HSP20 led to a time dependent loss of wrinkles (relaxation of the cells). This experiment demonstrates that transduction of phosphopeptide analogues of HSP20 also relaxes the cells.

Example 5

This experiment demonstrates that transduction of phosphopeptide analogues of HSP20 relax and prevent spasm in intact strips of vascular smooth muscle. Transverse strips of bovine carotid artery smooth muscle, denuded of endothelium, were suspended in a muscle bath containing bicarbonate buffer (120 mM NaCl, 4.7 mM KCl, 1.0 mM $MgSO_4$, 1.0 mM NaH_2PO_4, 10 mM glucose, 1.5 mM $CaCl_2$, and 25 mM Na_2HCO_3, pH 7.4), equilibrated with 95% O_2 / 5% CO_2, at 37°C at one gram of tension for 2 hours. The muscles were pre-contracted with serotonin (1 μM for 10 minutes) and cumulative doses of FITC-phosphoHSP20-TAT, FITC-scrambled phosphoHSP20-TAT (FITC-NH_2-βAGGGGYGRKKRRQRRRPRKS*LWALGRPLA-COOH, open circles) **(SEQ ID NO:305)**, or FITC-TAT (FITC- NH_2-βAGGGGYGRKKRRQRRR, closed triangles)

(SEQ ID NO:306) were added every 10 minutes. The force is depicted as a percentage of the maximal serotonin contraction (n = 5, * = $p < 0.05$ compared to 0 peptide added). Representative strips were fixed in 4% paraformaldehyde and examined under fluorescence microscopy (40X magnification). The internal elastic lamina (IEL) autofluoresced, and the media and adventitia (ADV) also displayed fluorescence(not shown).

The results of this Experiment are illustrated in **Figure 3**. Transduction of pre-contracted strips of intact bovine corotid artery smooth muscle with the FITC-TAT-HSP20 phosphopeptide led to a dose dependent decrease in serotonin pre-contracted muscles. Peptides containing the scrambled sequence or FITC-TAT alone had no significant effect on contractile force. This shows that the phosphopeptide analogues relax and prevent spasm in intact vascular smooth muscles. There was a diffuse fluorescence staining pattern of the muscle strips after transduction with the FITC-TAT-HSP20 phosphopeptide which shows that the peptides enter the muscles.

Example 6

This experiment shows that a different transducing peptide can introduce the HSP20 phosphopeptide analogues. In addition, it demonstrates that phosphopeptide analogues of HSP20 relax and prevent spasm in smooth muscles from a different vascular bed in a different species. Finally, it shows that transduction of HSP20 analogues relax and prevent spasm in muscles in which an intact endothelium is present.

Rings of porcine coronary artery in which the endothelium was **not** denuded, were suspended in a muscle bath containing bicarbonate buffer (120 mM NaCl, 4.7 mM KCl, 1.0 mM $MgSO_4$, 1.0 mM NaH_2PO_4, 10 mM glucose, 1.5 mM $CaCl_2$, and 25 mM Na_2HCO_3, pH 7.4), equilibrated with 95% O_2 / 5% CO_2, at 37^{o}C at one gram of tension for 2 hours. The muscles were pre-contracted with serotonin (1 μM for 10 minutes) and cumulative doses of PTD-pHSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH, closed circles) **(SEQ ID NO:307)** or PTD-scrambled-pHSP20 (NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH open circles) **(SEQ ID NO:308)** were added every 10 minutes (**Figure 4**). The percentage of relaxation is

depicted as a percentage of the maximal serotonin contraction ($n = 5$, $* = p < 0.05$ compared to 0 peptide added). The concentrations of peptide used are depicted on the x axis. Representative rings were treated with peptides (1 mM final concentration) linked to FITC (15 minutes at 37° C), fixed in 4% paraformaldehyde and examined under fluorescence microscopy (40X magnification).

The results of this experiment are illustrated in Figure 4. This shows that phosphopeptide analogues of HSP20 relax and prevent spasm in muscles from a different species and different vascular bed. There was marked fluorescence in the strips treated with protein transduction analogues. This demonstrates that a protein transduction peptide that is different than TAT can transduce the phosphopeptide analogue and relax and prevent spasm in muscles.

Example 7

This experiment shows that protein transduction of phosphopeptide analogues of HSP20 can relax and prevent spasm in non-vascular smooth muscles.

The internal anal sphincter was obtained from a human pathology specimen after an abdominal perineal resection for cancer. The smooth muscles were equilibrated in a muscle bath as described in example 6. The muscles developed tonic sustained contractions when warmed in the bicarbonate buffer. These contractions relaxed with the addition of the guanylate cyclase activator, sodium nitroprusside (SNP). When the sodium nitroprusside was washed out of the bath, the muscles again contracted spontaneously. The muscles were then treated with the PTD-phosphopeptide analogues of HSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH, 1 mM final concentration) (**SEQ ID NO:307**). The muscles relaxed and spasm was prevented in response to the phosphopeptide analogues and the relaxation was sustained.

Intestinal smooth muscle was obtained from the tinea coli of a pig. These muscles were equilibrated in a muscle bath as described in example 6. The muscles produced transient contractions in response to high extracellular potassium chloride (KCl 110 mM) and in response to carbachol (10^{-6} M). The muscles were then treated with a dextran gel containing the PTD-phosphopeptide analogues of HSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH, 1 mM final concentration)

(SEQ ID NO:307) and treated with carbachol. Treatment with the phosphopeptide analogues significantly attenuated the contractile response to carbachol.

Tracheal and corpra cavernosal smooth muscles were obtained from a New Zealand White rabbits after sacrifice. The muscles were equilibrated in a muscle bath as described in example 6. The tracheal muscles were pre-contracted with carbachol and the corpra cavernosal smooth muscles were pre-contracted with norepinephrine. The muscles were then treated with the PTD-phosphopeptide analogues of HSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH) (SEQ ID NO:307). Both the tracheal and the corpra cavernosal muscles relaxed and spasm was prevented in response to the phosphopeptide analogues.

The results of these experiments show that the phosphopeptide analogues of HSP20 relax and prevent spasm in human anal sphincter smooth muscles, porcine intestinal smooth muscle, rabbit tracheal smooth muscles, and rabbit corpra cavernosal smooth muscles.

Example 8

This experiment shows that protein transduction of phosphopeptide analogues of HSP20 can relax and prevent spasm in human saphenous vein smooth muscles.

Human saphenous vein was obtained from remnants that were discarded after vascular bypass operations. Rings of the saphenous vein were equilibrated in a muscle bath as described in experiment 4. The rings were treated with a 7.5% dextran gel alone, or a 7.5% dextran gel containing the phosphopeptide analogues of HSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH) (SEQ ID NO:307). The rings were then treated with serotonin (1 uM). The rings treated with the 7.5% dextran gel alone contracted in response to serotonin. However, the rings treated with the 7.5% dextran gel that contained the HSP20 phosphopeptide analogues did not contract in response to serotonin.

These results show that the phosphopeptide analogues of HSP20 prevent spasm (contraction) of human saphenous vein smooth muscles.

Example 9

This experiment was performed to demonstrate that smaller peptide analogues of phosphorylated HSP20 relax and prevent spasm of smooth muscles even more effectively than the larger analogues.

Rings of rabbit aorta in which the endothelium was **not** denuded, were suspended in a muscle bath containing bicarbonate buffer (120 mM NaCl, 4.7 mM KCl, 1.0 mM $MgSO_4$, 1.0 mM NaH_2PO_4, 10 mM glucose, 1.5 mM $CaCl_2$, and 25 mM Na_2HCO_3, pH 7.4), equilibrated with 95% O_2 / 5% CO_2, at 37°C at one gram of tension for 2 hours. The rings were pre-contracted with norepinephrine (10^{-7} M) and treated with RRRRRRApSAPLP (**SEQ ID NO:309**) or RRRRWLRRApSAPLP (**SEQ ID NO:310**). Both peptides caused rapid and complete relaxation and inhibition of spasm of the muscles, and the relaxation was faster and the muscles remained in a relaxed state for longer than when the longer peptides were used. The peptides used were prepared by Fmoc-based peptide synthesis, and the peptides retained the Fmoc moiety at the amino terminus of the peptide.

These data show that poly arginine sequences can transduce the HSP20 analogues and induce relaxation and that the smaller sequence ApSAPLP (**SEQ ID NO:3**) (where "p' indicates that the S residue is phosphorylated) causes rapid and complete relaxation and inhibition of spasm.

Example 10

This experiment illustrates that HSP20 is expressed in mesangial cells and in rat aortic smooth muscle cells that have been stably transfected with PKG. It also illustrates that relaxation of mesangial cells is associated with increases in the phosphorylation of HSP20.

Homogenates of mesangial cells (**Figure 5**, lane 1), rat aortic smooth muscle cells (**Figure 5**, lane 2), and PKG transfected rat aortic smooth muscle cells (**Figure 5**, lane 3) were immunoblotted for PKG (**Figure 5**, panel A) or HSP20 (**Figure 5**, panel B). In a separate experiment, mesangial cells were untreated (**Figure 5**, panel C) or treated with dibutyryl cAMP (10 μM, 15 minutes, **Figure 5**, panel D). The proteins were separated by 2-dimensional electrophoresis, transferred to immobilon and probed with anti-HSP20 antibodies. Increases in the phosphorylation of HSP20

lead to a shift in the electrophoretic mobility of the protein to a more acidic isoform (arrow).

These data show that activation of cyclic nucleotide-dependent signaling pathways in mesangial cells (as shown in Figure 2) is associated with phosphorylation of HSP20.

Example 11

This experiment illustrates that cells expressing HSP20 (stably PKG transfected cells) are able to contract.

Rat aortic smooth muscle cells that are multiply passaged or that stably express PKG were cultured on a silicone substrata in the presence of serum. The cells were imaged with phase contrast microscopy (10X magnification). The multiply passaged cells did not form wrinkles on the substrata whereas the PKG transfected cells formed wrinkles. To determine if the wrinkles were reversible, PKG transfected cells were treated with dibutyryl cAMP (10 uM) for 30 minutes. Dibutyryl cAMP led to a decrease in wrinkle formation.

Taken together with example 10, these results show that the expression of HSP20 is associated with a contractile phenotype. Vascular smooth muscle cells exist in widely divergent phenotypes. In the normal vessel wall, the smooth muscle cells are in a well differentiated contractile phenotype and are capable of generating force. In response to injury, or cell culture conditions, the cells modulate to a synthetic or secretory phenotype. These cells proliferate and secrete matrix proteins contributing to intimal hyperplasia. Phenotypic modulation is associated with changes in gene expression, protein expression, morphology, and physiologic responses. This leads to pathologic narrowing of the vessel lumen which occurs in atherosclerosis and intimal hyperplasia. This leads to stenotic lesions and ultimately occlusion of the vessel. Thus, maintaining expression of HSP20 is important for the maintenance of the contractile phenotype.

Example 12

Cellular processes such as cell adhesion, cytokinesis, cell motility, migration, and contraction all require dynamic reorganization of the actin cytoskeleton These experiments show that the phosphorylation of HSP20 modulates changes in these actin filaments.

Transfected mesangial cells were fixed and the actin filaments were stained with fluorescent-labeled phalloidin. Mesangial cells were transfected with EGFP alone (EGFP), S16A-HSP20 (MUT-EGFP, or wild type HSP20 (WT-EGFP). The cells were plated on a glass slides, and not treated (CONT) or treated with dibutyryl cAMP (10 μM, for 30 minutes, db-cAMP). The cells were fixed and stained with rhodamine phalloidin. Dibutyryl cAMP led to a loss of central actin stress fibers in EGFP but not S16A-HSP20 cells. In the cells overexpressing HSP20 the actin fibers were peripherally localized. The results of this experiment are illustrated in **Figure 6.**

These experiments show that activation of cyclic nucleotide-dependent signaling pathways, which lead to increases in the phosphorylation of HSP20, are associated with a loss of central actin stress fibers. Over-expression of HSP20 was also associated with a loss of actin stress fibers. In cells overexpressing a mutated form of HSP20 in which the serine has been replaced with an alanine (S16A-HSP20) and cannot be phosphorylated, there is no loss of these central actin fibers with activation of cyclic nucleotide-dependent signaling pathways. These studies demonstrate that phosphorylation of HSP20 is associated with changes in actin fiber formation.

Example 13

This experiment shows that protein transduction of smooth muscle cells with phosphopeptide analogues of HSP20 also leads to changes in actin fiber formation.

Rat aortic smooth muscle cells were treated with lyophosphatidic acid (LPA) in the presence and absence of FITC-TAT-pHSP20 (FITC -NH_2-βAGGGGYGRKKRRQRRRWLRRAS*APLPGLK-COOH, 50 uM) **(SEQ ID NO:307)** Lysophosphatidic acid (LPA) is a substance which promotes actin fiber formation. Inhibition of the actions of LPA have been shown to inhibit intimal hyperplasia.

The cells were fixed and stained with phalloidin and images were obtained with confocal microscopy. LPA led to robust actin stress fiber formation, whereas there was a loss of central actin stress fibers in the cells treated with LPA in the presence of the FITC-TAT-pHSP20 peptide. These studies show that protein transduction with the phosphopeptide analogues of HSP20 inhibit LPA-induced actin

fiber formation. These studies confirm that HSP20 has a direct role in modulating actin fiber formation.

Example 14

Cell adhesion formation involves the interaction between integrins and extracellular matrix substrates. This induces integrin clustering. The cells then form actin microfilaments and the cells spread. If the appropriate signals are provided by the matrix, the cells proceed to organize their cytoskeleton as characterized by the formation of focal adhesions and actin-containing stress fibers. Cell adhesion is a dynamic reversible process integral to cell migration. Activation of cGMP leads to focal adhesion disassembly. These studies show that phosphopeptide analogues of HSP20 mediate focal adhesion disassembly.

Bovine aortic endothelial cells were plated on glass coverslips (80K-100K cells) in DMEM plus 10 % FBS over night (24 wells plate). The cells were serum starved (no serum) for one hour and incubated in the presence of the peptide analogues of HSP20 [NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH - pHSP20 (10 uM) **(SEQ ID NO:307)** or scrambled analogues of HSP20 [NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH -scHSP20 (10 uM)] **(SEQ ID NO:308)** for 30 minutes. The cells were fixed with 3% glutaraldehyde and the number of focal adhesions was detected with interference reflection microscopy. The Hep I peptide was used as a positive control. This peptide binds to the heparin binding site of thrombospondin in induces focal adhesion disassembly. Both Hep I and pHSP20 led to focal adhesion disassembly. The results are illustrated in **Figure 7**.

Treatment with PTD-pHSP20 led to a disassociation of focal adhesions similar to the disassociation induced by a peptide from the amino-terminal heparin-binding domain of thrombospondin 1 (Hep 1). The scrambled peptide had no significant effect on focal adhesion disassembly. These studies show that phosphorylated HSP20 mediates focal adhesion disassembly. This weakens cell attachment and prevents the formation of the attachments necessary for cell migration.

Example 15

This Experiment shows that the phosphorylated peptide analogues of HSP20 directly inhibit cell migration.

Confluent A10 cells were serum starved (0.5% fetal bovine serum, FBS) for 48 hours. A linear wound was made in the smooth muscle cell monolayer using a rubber scraper and the scratched edges were marked using metal pins. The cells were changed to 10% FBS media containing PTD-pHSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH **(SEQ ID NO:307)**, or PTD-scrambled-pHSP20 (NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH **(SEQ ID NO:308)** (50 μM) and incubated for 24 hours. The cells were fixed and stained with hematoxylin. The number of cells migrating into a 1 cm^2 scratched area were counted as an index for migration. In additional experiments, the migration of A10 cells was determined in a Boyden chamber assay. In both cases the phosphopeptide analogue of HSP20 led to inhibition of migration. **Figure 8** illustrates the results of these experiments.

These results show that transduction of phosphopeptide analogues of HSP20 inhibits serum-induced migration of smooth muscle cells.

Example 16

This experiment shows that transduction of phosphopeptide analogues of HSP20 inhibits serum-induced proliferation of smooth muscle cells.

A10 cells were serum starved for 3 days. The cells were then treated with media containing 10% fetal bovine serum, PTD-pHSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH **(SEQ ID NO:307)**, or PTD-scrambled-pHSP20 (NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH **(SEQ ID NO:308)** (50 μM). After 24 hours cell counts were performed. The number of cells per well in the serum starved plates averaged 109 cells/well (+/- 7.4) compared to 276 +/- 6.1 in wells containing 10% fetal bovine serum (FBS). In the presence of FBS, the phosphopeptide analogues of HSP20 containing a transduction domain inhibited of smooth muscle proliferation, 149 +/- 14.6 compared to transduction of the scrambled phosphopeptide analogue of HSP20 (242.3 +/- 15.3 cells/well). The results of these experiments are illustrated in **Figure 9**.

The results from these examples demonstrate that HSP20 is associated with a contractile phenotype and that transduction of phosphopeptide analogues of HSP20 inhibit actin fiber formation, focal adhesion formation, smooth muscle cell migration

and smooth muscle proliferation. These are cellular processes that lead to intimal hyperplasia, and other disorders as discussed throughout the application.

Example 17

These experiments show that HSP20 inhibits intimal hyperplasia in human saphenous vein grafts.

Segments of human saphenous vein were cultured in media containing 30% fetal bovine serum. The segments were treated for 14 days with media containing serum alone, serum and the phosphopeptide analogue of HSP20 (PTD-pHSP20 (NH_2-βAYARRAAARQARAWLRRAS*APLPGLK-COOH, 10 μM) **(SEQ ID NO:307)**, or the PTD-scrambled phosphopeptide analogue (NH_2-βAYARRAAARQARAPRKS*LWALGRPLA-COOH, 10 μμM). **(SEQ ID NO:308)** The rings were fixed in formalin, stained with hematoxylin and eosin, and the intimal area was measured morphometrically. There was a significant reduction in intimal area in the rings transduced with the phosphopeptide analogues of HSP20 compared to the rings treated with serum alone or serum and transduction of the scrambled analogue.

These results show that intimal hyperplasia can be inhibited in human saphenous vein segments by transduction of the phosphopeptide analogues of HSP20.

Example 18

This Experiment illustrates that plant cells can be engineered to produce recombinant HSP20.

Tobacco BY-2 cells were transformed with vector alone (vector transformed) or with His tagged HSP20 constructs (6Xhis-HSP20 transformed). Western blots were performed on cells lysates using anti-6Xhis monoclonal antibodies. There is immunoreactivity of a 20 kDa polypeptide in the HSP20 lysates but not the empty vector transformed lysates.

Optical sections from confocal immunofluorescence images of processed tobacco cells transiently-expressing either myc-epitope tagged HSP20, probed with anti-myc antibodies, HSP20, probed with anti-HSP20 antibodies, TAT-HSP20,

probed with anti-HSP20 antibodies, or HISTAT-HSP20, probed with anti-his antibodies. Expression is present with all 4 constructs (bar = 100μm).

These data show that plants can be engineered to produce proteins that contain a protein transduction sequence and the HSP20 molecule. This represents an alternative source of production of HSP20.

We claim:

1. A polypeptide consisting of a sequence according to general formula I:

X1-X2-[X3-A(X4)APLP-X5-]$_u$-X6

wherein X1 is absent or is one or more molecules comprising one or more aromatic ring;

X2 is absent or comprises a transduction domain;

X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (**SEQ ID NO:1**);

X4 is selected from the group consisting of S, T, Y, D, E, phosphoserine analogs and phosphotyrosine analogs;

X5 is 0, 1, 2,or 3 amino acids of a sequence of genus Z1-Z2-Z3,

wherein Z1 is selected from the group consisting of G and D;

Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S and T; and

X6 is absent or comprises a transduction domain; and

wherein u is 1-5.

2. The polypeptide of claim 1 wherein X4 is S.

3. The polypeptide of claim 1 wherein X4 is T.

4. The polypeptide of claim 1 wherein X4 is Y.

5. The polypeptide of any one of claims 1-4, wherein X3 is R.

6. The polypeptide of any one of claims 1-4, wherein X3 is RR.

7. The polypeptide of any one of claims 1-4, wherein X3 is LRR (**SEQ ID NO:311**).

8. The polypeptide of any one of claims 1-4, wherein X3 is WLRR (**SEQ ID NO:1**)

9. The polypeptide of any one of claims 1-8, wherein X5 is G.

10. The polypeptide of any one of claims 1-8, wherein X5 is D.

11. The polypeptide of any one of claims 1-8, wherein X5 is GL.

12. The polypeptide of any one of claims 1-8, wherein X5 is GK.

13. The polypeptide of any one of claims 1-8, wherein X5 is DL.

14. The polypeptide of any one of claims 1-8, wherein X5 is DK.

15. The polypeptide of any one of claims 1-8, wherein X5 is GLS (**SEQ ID NO:312**).

16. The polypeptide of any one of claims 1-8, wherein X5 is GLT (**SEQ ID NO:313**).

17. The polypeptide of any one of claims 1-8, wherein X5 is GKS (SEQ ID NO:314).

18. The polypeptide of any one of claims 1-8, wherein X5 is GKT (SEQ ID NO:315).

19. The polypeptide of any one of claims 1-8, wherein X5 is DLS (SEQ ID NO:316).

20. The polypeptide of any one of claims 1-8, wherein X5 is DLT (SEQ ID NO:317).

21. The polypeptide of any one of claims 1-8, wherein X5 is DKS (SEQ ID NO:318)

22. The polypeptide of any one of claims 1-8, wherein X5 is DKT (SEQ ID NO:319)

23. The polypeptide of any one of claims 1-22 wherein X1 is a molecule comprising an aromatic ring.

24. The polypeptide of claim 23 wherein X1 is selected from the group consisting of F, Y, W; and compounds comprising 9-fluroenylmethyl.

25. The polypeptide of any one of claims 1-24 wherein X2 comprises a transduction domain.

26. The polypeptide of any one of claims 1-24 wherein X6 comprises a transduction domain.

27. The polypeptide of any one of claims 1-24 wherein both X2 and X6 comprise a transduction domain.

28. The polypeptide of any one of claims 1-27 wherein X4 is phosphorylated.

29. The polypeptide of any one of claims 1-28 wherein the transduction domain is selected from group consisting of: $(R)_{4-9}$ (SEQ ID NO:279); GRKKRRQRRRPPQ (SEQ ID NO:280); AYARAAARQARA (SEQ ID NO:281); DAATATRGRSAASRPTERPRAPARSASRPRRPVE (SEQ ID NO:282); GWTLNSAGYLLGLINLKALAALAKKIL (SEQ ID NO:283); PLSSIFSRIGDP (SEQ ID NO:284); AAVALLPAVLLALLAP (SEQ ID NO:285); AAVLLPVLLAAP (SEQ ID NO:286); VTVLALGALAGVGVG (SEQ ID NO:287); GALFLGWLGAAGSTMGAWSQP (SEQ ID NO:288); GWTLNSAGYLLGLINLKALAALAKKIL (SEQ ID NO:289); KLALKLALKALKAALKLA (SEQ ID NO:290); KETWWETWWTEWSQPKKKRKV (SEQ ID NO:291); KAFAKLAARLYRKAGC

(**SEQ ID NO:292**); KAFAKLAARLYRAAGC (**SEQ ID NO:293**); AAFAKLAARLYRKAGC (**SEQ ID NO:294**); KAFAALAARLYRKAGC (**SEQ ID NO:295**); KAFAKLAAQLYRKAGC (**SEQ ID NO:296**), and AGGGGYGRKKRRQRRR (**SEQ ID NO:306**).

30. A polypeptide comprising a sequence according to general formula II:

$$X1\text{-}X2\text{-}[X3\text{-}A(X4)APLP\text{-}X5]_n\text{-}X6$$

wherein X1 is absent or is one or more molecules comprising one or more aromatic ring;

X2 is absent or comprises a cell transduction domain;

X3 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of **SEQ ID NO:297**;

X4 is selected from the group consisting of S, T, Y, D, E, phosphoserine analogs and phosphotyrosine analogs;

X5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160 of **SEQ ID NO:297**;

X6 is absent or comprises a cell transduction domain; and

wherein at least one of X2 and X6 comprise a transduction domain.

31. The polypeptide of claim 30 wherein X4 is S.

32. The polypeptide of claim 30 wherein X4 is T.

33. The polypeptide of claim 30 wherein X4 is Y.

34. The polypeptide of claim 30, wherein the polypeptide comprises a polypeptide with an amino acid sequence selected from the group consisting of: X1-X2-**SEQ ID NO:297**-X6; X1-X2-**SEQ ID NO:298**-X6; X1-X2-**SEQ ID NO:299**-X6; X1-X2-**SEQ ID NO:300**-X6; X1-X2-**SEQ ID NO:301**-X6; and X1-X2-**SEQ ID NO:302**-X6.

35. The polypeptide of any one of claims 30-34 wherein both X2 and X6 comprise a transduction domain.

36. The polypeptide of any one of claims 30-33 and 35 wherein X4 is phosphorylated.

37. The polypeptide of claim 34, wherein the polypeptide is phosphorylated.

38. The polypeptide of any one of claims 30-37 wherein X1 is a molecule comprising an aromatic ring.

39. The polypeptide of claim 38 wherein X1 is selected from the group consisting of F, Y, W; and compounds comprising 9-fluroenylmethyl.

40. The polypeptide of any one of claims 30-39 wherein the transduction domain is selected from group consisting of: $(R)_{4-9}$ (SEQ ID NO:279); GRKKRRQRRRPPQ (SEQ ID NO:280); AYARAAARQARA (SEQ ID NO:281); DAATATRGRSAASRPTERPRAPARSASRPRRPVE (SEQ ID NO:282); GWTLNSAGYLLGLINLKALAALAKKIL (SEQ ID NO:283); PLSSIFSRIGDP (SEQ ID NO:284); AAVALLPAVLLALLAP (SEQ ID NO:285); AAVLLPVLLAAP (SEQ ID NO:286); VTVLALGALAGVGVG (SEQ ID NO:287); GALFLGWLGAAGSTMGAWSQP (SEQ ID NO:288); GWTLNSAGYLLGLINLKALAALAKKIL (SEQ ID NO:289); KLALKLALKALKAALKLA (SEQ ID NO:290); KETWWETWWTEWSQPKKKRKV (SEQ ID NO:291); KAFAKLAARLYRKAGC (SEQ ID NO:292); KAFAKLAARLYRAAGC (SEQ ID NO:293); AAFAKLAARLYRKAGC (SEQ ID NO:294); KAFAALAARLYRKAGC (SEQ ID NO:295); KAFAKLAAQLYRKAGC (SEQ ID NO:296), and AGGGGYGRKKRRQRRR (SEQ ID NO:306).

41. A pharmaceutical composition, comprising one or more polypeptides according to any one of claims 1 to 40, and a pharmaceutically acceptable carrier.

42. An isolated nucleic acid sequence encoding the polypeptide of any one of claims 1-40.

43. An expression vector comprising the nucleic acid of claim 42.

44. A host cell comprising the expression vector of claim 43.

45. An improved biomedical device, wherein the biomedical device comprises one or more polypeptides according to any one of claims 1 to 40 disposed on or in the biomedical device.

46. The improved biomedical device of claim 45 wherein the biomedical device is selected from the group consisting of stents, grafts, shunts, and fistulas.

47. The improved biomedical device of claim 44 or 45, further comprising an HSP27 inhibitor disposed on or in the biomedical device.

48. A method for inhibiting smooth muscle cell proliferation and/or migration, comprising contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of one or more polypeptides according to any one of claims 1 to 40.

49. A method for inhibiting smooth muscle cell proliferation and/or migration, comprising contacting the smooth muscle cells with an amount effective to inhibit smooth muscle cell proliferation and/or migration of HSP20, or a functional equivalent thereof.

50. The method of claim 48 or 49, wherein the contacting occurs in vivo.

51. The method of claim 50 wherein the method is used to treat or prevent a disorder selected from the group consisting of intimal hyperplasia, stenosis, restenosis, transplant vasaculopathy, and atherosclerosis.

52. The method of claim 51, wherein the method is performed on a subject who has undergone, is undergoing, or will undergo a procedure selected from the group consisting of angioplasty, vascular stent placement, endarterectomy, atherectomy, bypass surgery, vascular grafting, organ transplant, prosthetic implant emplacement, microvascular reconstructions, plastic surgical flap construction, and catheter emplacement.

53. The method of claim 50 wherein the method is used to treat smooth muscle cell tumors.

54. The method of claim 53 wherein the smooth muscle cell tumor is a leiomyosarcoma.

55. The method of any one of claims 48-54 wherein the method further comprises contacting the smooth muscle cells with an inhibitor of HSP27.

56. The method of any one of claims 48-55 wherein the contacting comprises contacting a blood vessel.

57. A method for treating or inhibiting a disorder selected from the group consisting of intimal hyperplasia, stenosis, restenosis, and/or atherosclerosis, comprising contacting a subject in need thereof with an amount effective to treat or inhibit intimal hyperplasia, stenosis, restenosis, and/or atherosclerosis of one or more polypeptides according to any one of claims 1-40.

58. A method for treating or inhibiting a disorder selected from the group consisting of intimal hyperplasia, stenosis, restenosis, and/or atherosclerosis, comprising contacting a patient in need thereof with an amount effective to treat or inhibit intimal hyperplasia, stenosis, restenosis, and/or atherosclerosis of HSP20,or a functional equivalent thereof.

59. The method of claim 57 or 58, wherein the subject has undergone, is undergoing, or will undergo a procedure selected from the group consisting of

angioplasty, vascular stent placement, endarterectomy, atherectomy; bypass surgery; vascular grafting; organ transplant; and catheter emplacement.

60. The method of any one of claims 57-59 wherein the method further comprises contacting the smooth muscle cells with an inhibitor of HSP27.

61. The method of any one of claims 57-60 wherein the contacting comprises contacting a blood vessel.

62. A method for treating or inhibiting smooth muscle spasm, comprising contacting a subject in need thereof with an amount effective to inhibit vasoconstriction of one or more polypeptides according to any one of claims 1 to 40.

63. A method for treating or inhibiting smooth muscle spasm, comprising contacting a subject in need thereof with an amount effective to inhibit vasoconstriction of HSP20, or a functional equivalent thereof.

64. The method of claim 62 or 63, wherein the method is used to treat or prevent vasospasm.

65. The method of claim 64 wherein the vasospasm is associated with a disorder or condition selected from the group consisting of angina, coronary vasospasm, Prinzmetal's angina, coronary ischemia, stroke, bradycardia hypertension, pulmonary (lung) hypertension, asthma (bronchospasm), toxemia of pregnancy, pre-term labor, pre-eclampsia/eclampsia, Raynaud's disease, Raynaud's phenomenon, hemolytic-uremia, non-occlusive mesenteric ischemia, anal fissure, achalasia, impotence, migraine, ischemic muscle injury associated with smooth muscle spasm, and vasculopathy.

66. The method of any one of claims 62-65 wherein the method further comprises contacting the smooth muscle cells with an inhibitor of HSP27.

67. The method of any one of claims 62-66 wherein the contacting comprises contacting a blood vessel.

68. A composition comprising:

(a) a polypeptide according to any one of claims 1-40; and

(b) an inhibitor of HSP27.

69. A method for inhibiting smooth muscle spasm, comprising contacting a graft with an amount effective to inhibit vasoconstriction of one or more polypeptides according to any one of claims 1 to 40.

70. A method for inhibiting smooth muscle spasm, comprising contacting a graft with an amount effective to inhibit vasoconstriction of HSP20, or a functional equivalent thereof.

71. The method of claim 69 or 70 wherein the method is used to inhibit vasospasm.

72. The method of claim 69 or 70 wherein the method is used to inhibit intimal hyperplasia.

FIGURE 1:

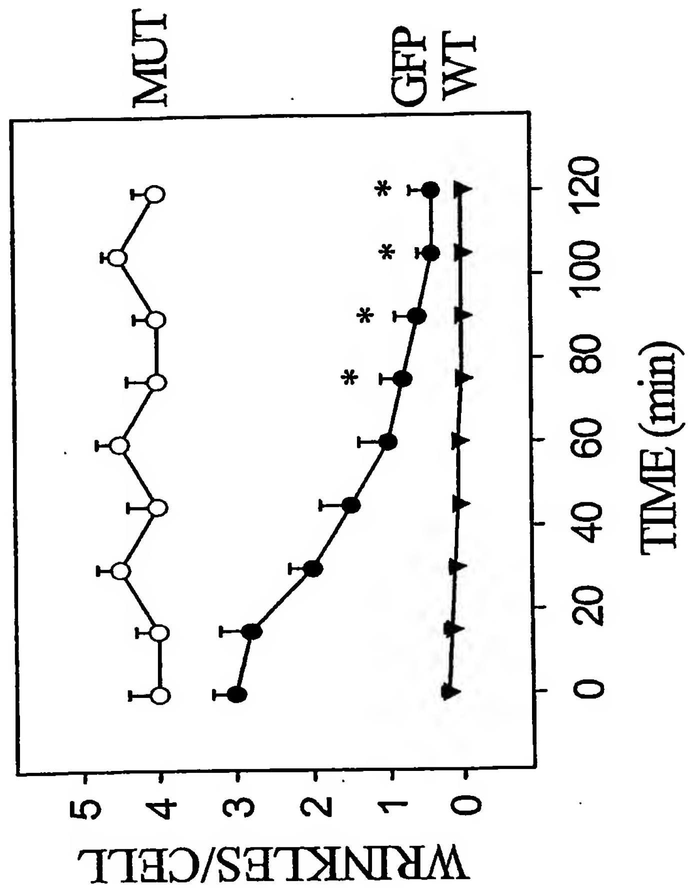
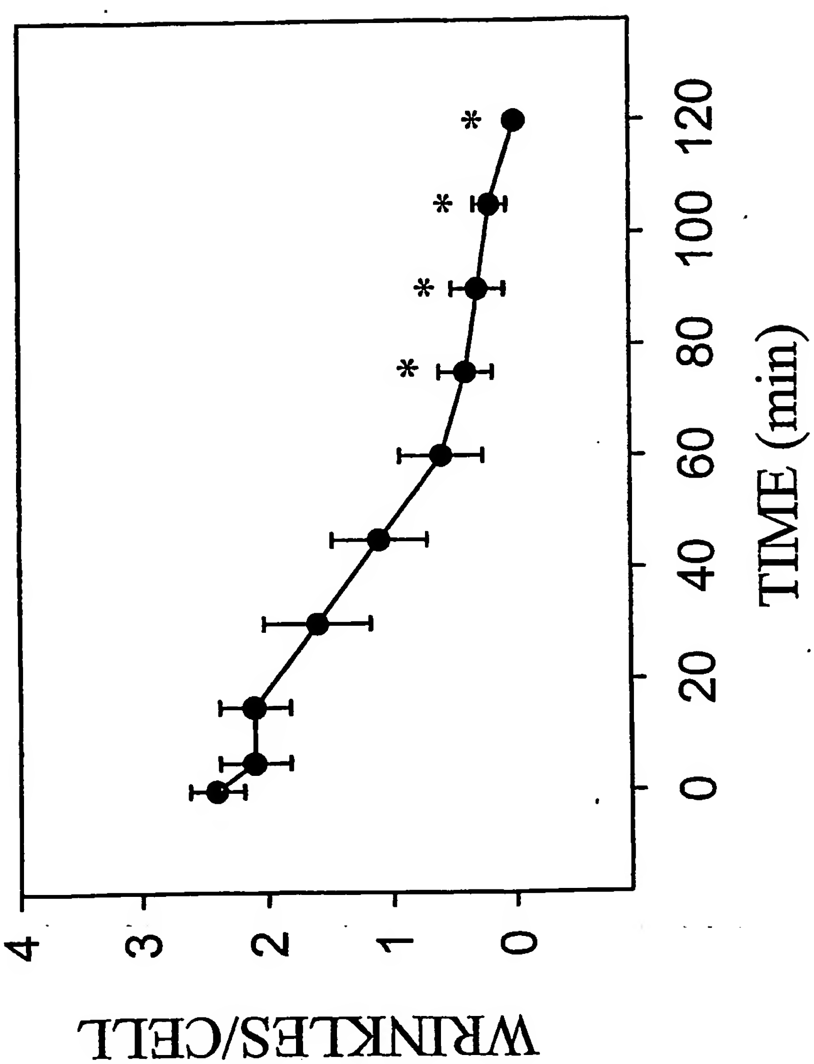


FIGURE 2:



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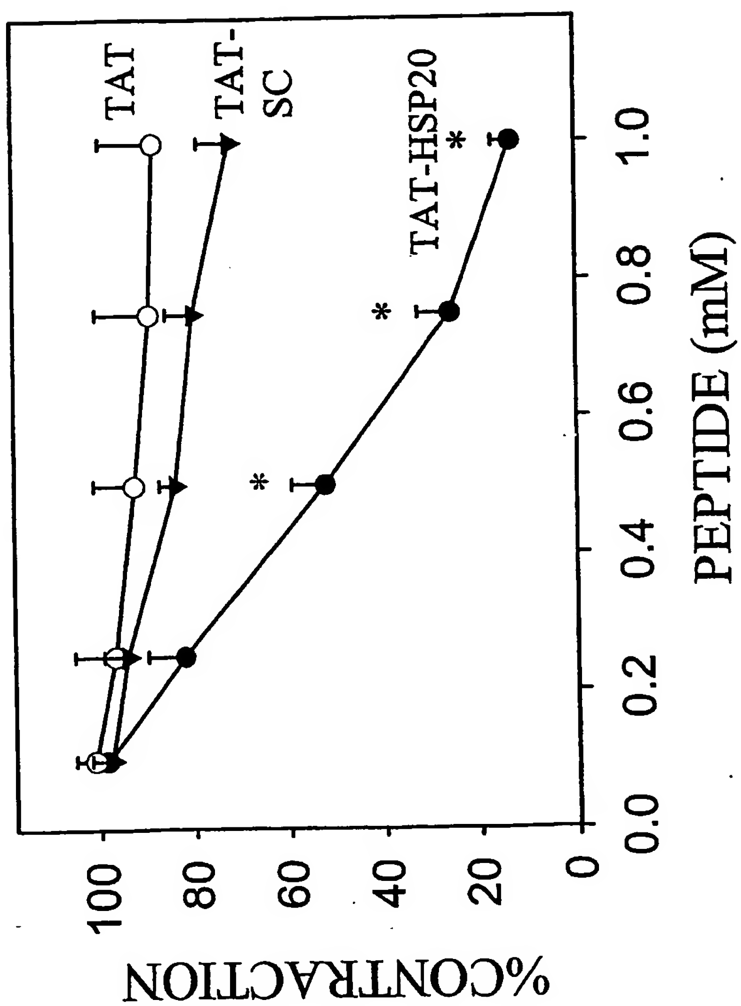
TAT
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TAT-HSP20
*
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20
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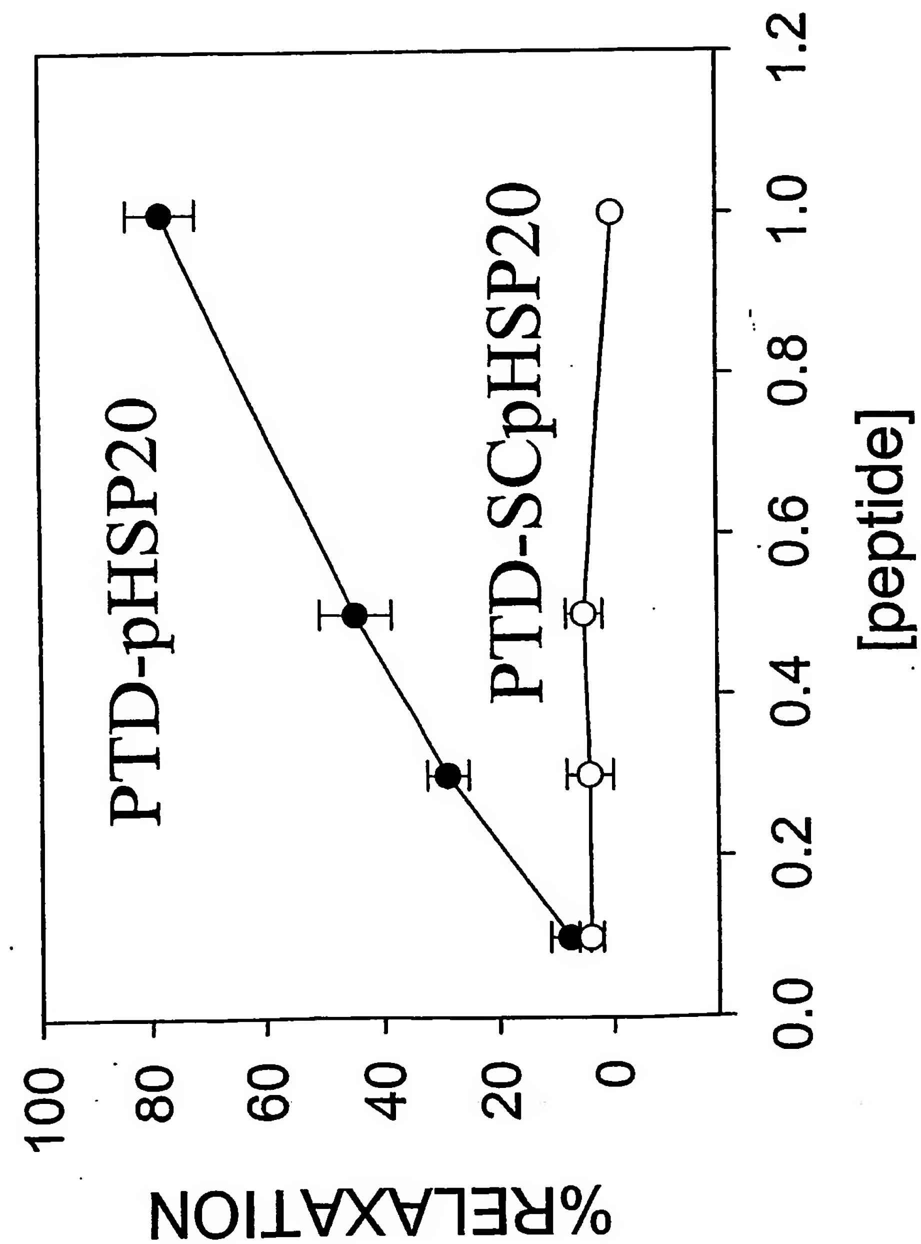
0.4
0.6
0.8
1.0

FIGURE 4: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PTD-SCpHSP20
%RELAXATION
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80
100
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0.8
1.0
1.2

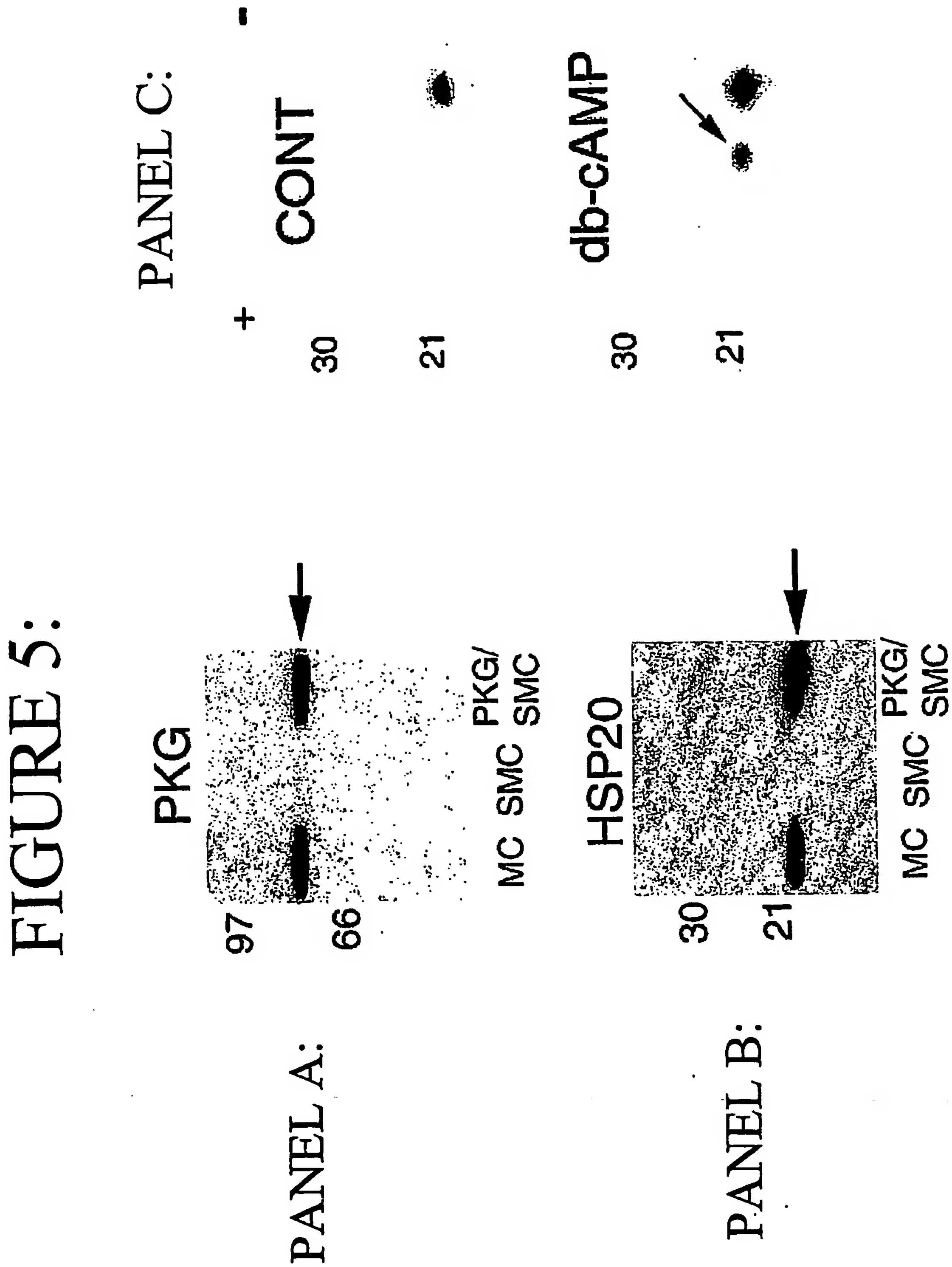
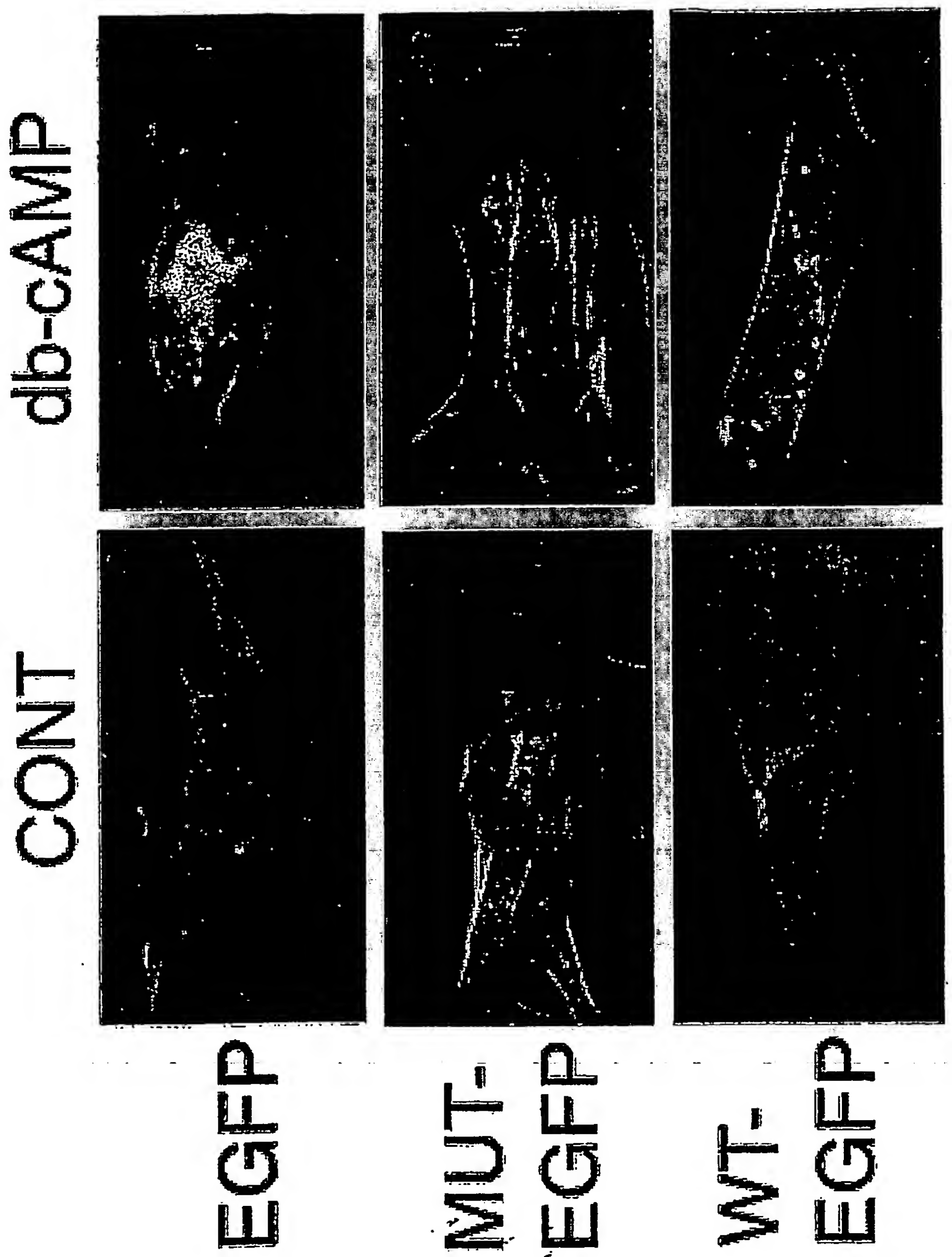


FIGURE 5:
PANEL A:
PKG
97
66
MC SMC PKG/SMC
PANEL B:
HSP20
30
21
MC SMC PKG/SMC
PANEL C:
+
-
CONT
30
21
db-cAMP
30
21

FIGURE 6:



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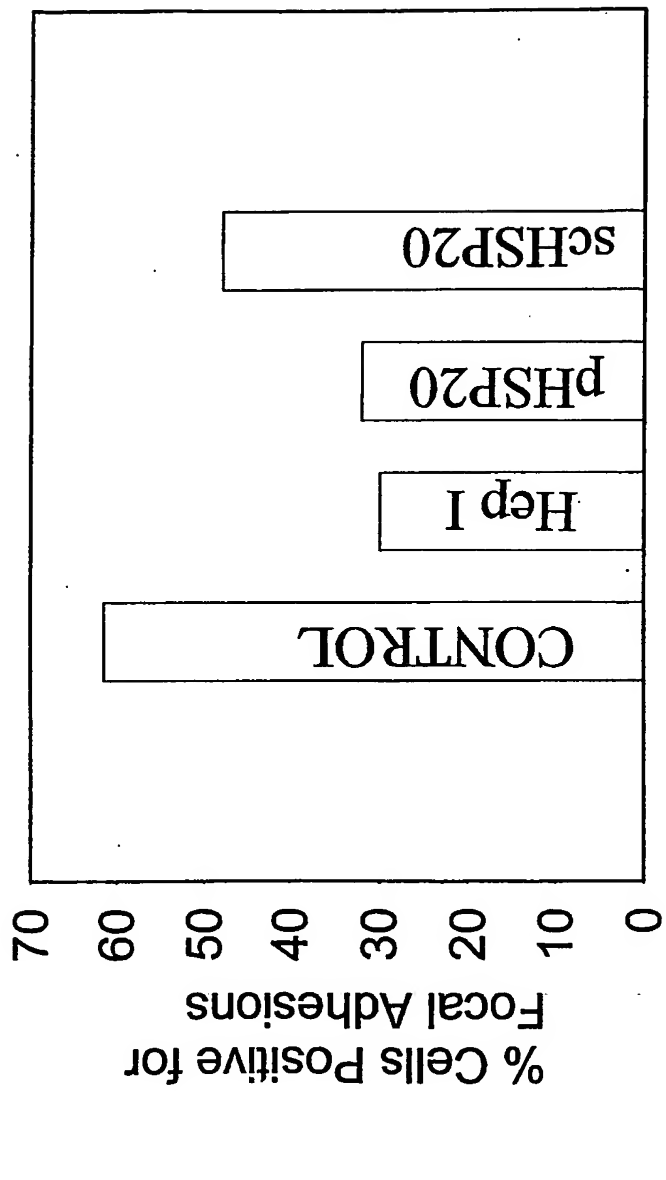
CONTROL
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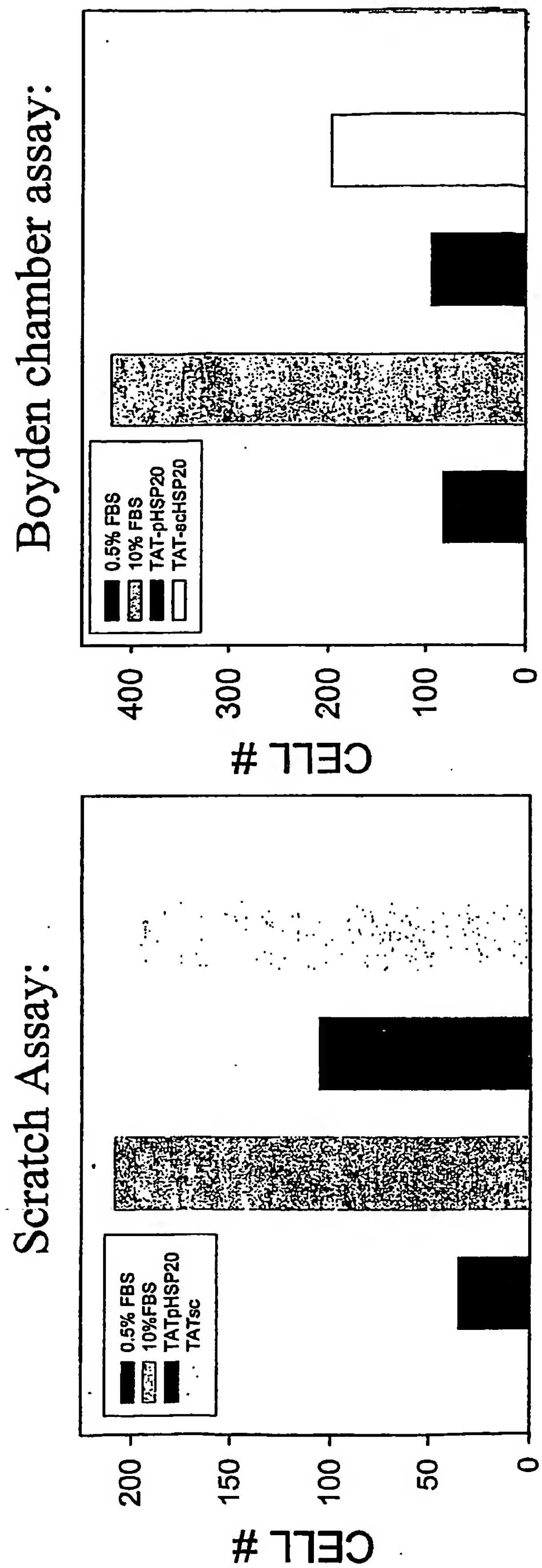
pHSP20
scHSP20
0
10
20
30
40
50
60
70
% Cells Positive for
Focal Adhesions

FIGURE 8:


Boyden chamber assay:
0.5% FBS
10% FBS
TAT-pHSP20
TAT-scHSP20
CELL #
400
300
200
100
0
Scratch Assay:
0.5% FBS
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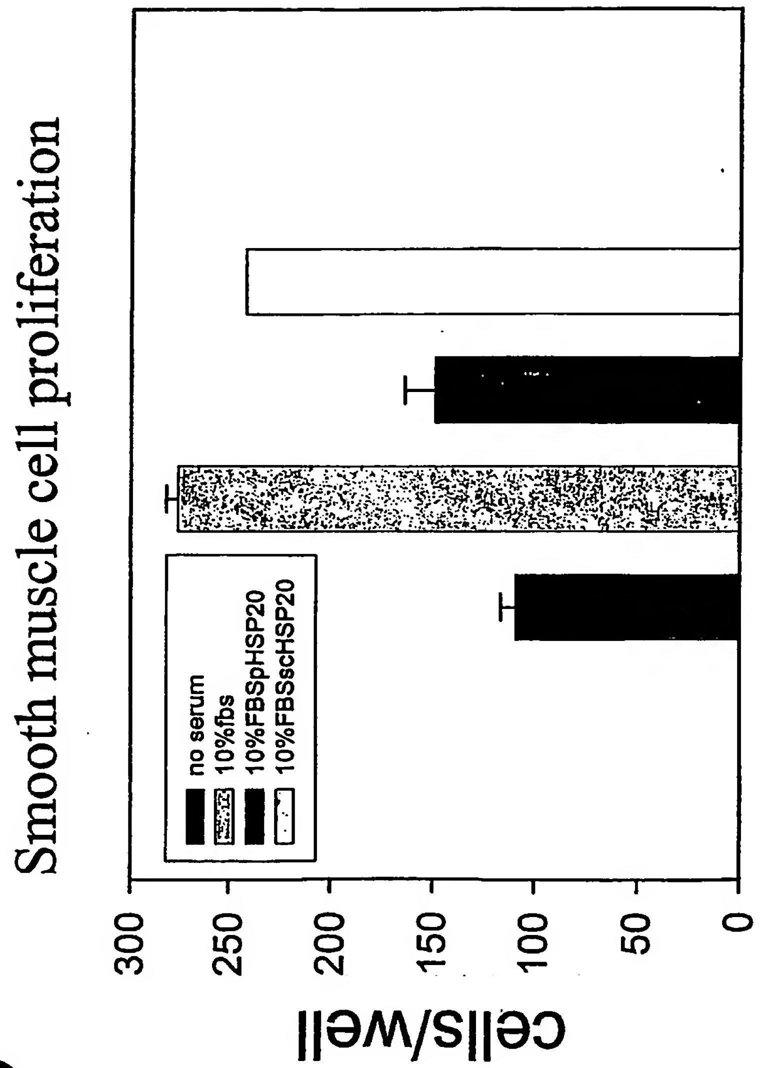
TATpHSP20
TATsc
CELL #
200
150
100
50
0

Figure 9


Smooth muscle cell proliferation
cells/well
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250
200
150
100
50
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no serum
10%fbs
10%FBSpHSP20
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Panitch, Alyssa
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<221> MISC_FEATURE

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<211> 13

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Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln
1 5 10

<210> 281

<211> 12

<212> PRT

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<400> 281

Ala Tyr Ala Arg Ala Ala Ala Arg Gln Ala Arg Ala
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<210> 282

<211> 34

<212> PRT

<213> Artificial sequence

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<223> Synthetic peptide

<400> 282

Asp Ala Ala Thr Ala Thr Arg Gly Arg Ser Ala Ala Ser Arg Pro Thr
1 5 10 15

Glu Arg Pro Arg Ala Pro Ala Arg Ser Ala Ser Arg Pro Arg Arg Pro
20 25 30

Val Glu

<210> 283

<211> 27

<212> PRT

<213> Artificial sequence

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<223> Synthetic peptide

<400> 283

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Leu Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 284

<211> 12

<212> PRT

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<223> Synthetic peptide

<400> 284

Pro Leu Ser Ser Ile Phe Ser Arg Ile Gly Asp Pro
1 5 10

<210> 285

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 285

Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro
1 5 10 15

<210> 286

<211> 12

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<223> Synthetic peptide

<400> 286

Ala Ala Val Leu Leu Pro Val Leu Leu Ala Ala Pro
1 5 10

<210> 287

<211> 15

<212> PRT

<213> Artificial sequence

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<223> Synthetic peptide

<400> 287

Val Thr Val Leu Ala Leu Gly Ala Leu Ala Gly Val Gly Val Gly
1 5 10 15

<210> 288

<211> 21

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 288

Gly Ala Leu Phe Leu Gly Trp Leu Gly Ala Ala Gly Ser Thr Met Gly
1 5 10 15

Ala Trp Ser Gln Pro
20

<210> 289

<211> 27

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 289

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Leu Ile Asn Leu
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu
20 25

<210> 290

<211> 18

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 290

Lys Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys
1 5 10 15

Leu Ala

<210> 291

<211> 21

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 291

Lys Glu Thr Trp Trp Glu Thr Trp Trp Thr Glu Trp Ser Gln Pro Lys
1 5 10 15

Lys Lys Arg Lys Val
20

<210> 292

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 292

Lys Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 293

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 293

Lys Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Ala Ala Gly Cys
1 5 10 15

<210> 294

<211> 16

<212> PRT

<213> Artificial sequence

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<223> Synthetic peptide

<400> 294

Ala Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 295

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 295

Lys Ala Phe Ala Ala Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 296

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 296

Lys Ala Phe Ala Lys Leu Ala Ala Gln Leu Tyr Arg Lys Ala Gly Cys
1 5 10 15

<210> 297

<211> 160

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 297

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Ser
1 5 10 15

Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg
20 25 30

Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr
35 40 45

Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val
50 55 60

Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val
65 70 75 80

Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His
85 90 95

Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe
100 105 110

Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp
115 120 125

Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile
130 135 140

Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys
145 150 155 160

<210> 298

<211> 160

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 298

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Asp
1 5 10 15

Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg
20 25 30

Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr
35 40 45

Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val
50 55 60

Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val
65 70 75 80

Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His
85 90 95

Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe
100 105 110

Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp
115 120 125

Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile
130 135 140

Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys
145 150 155 160

<210> 299

<211> 160

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 299

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Glu
1 5 10 15

Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg
20 25 30

Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr
35 40 45

Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val
50 55 60

Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val
65 70 75 80

Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His
85 90 95

Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe
100 105 110

Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp

115 120 125

Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile
130 135 140

Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys
145 150 155 160

<210> 300

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 300

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu Lys
1 5 10

<210> 301

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 301

Trp Leu Arg Arg Ala Asp Ala Pro Leu Pro Gly Leu Lys
1 5 10

<210> 302

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 302

Trp Leu Arg Arg Ala Glu Ala Pro Leu Pro Gly Leu Lys
1 5 10

<210> 303

<211> 486

<212> DNA

<213> Artificial sequence

<220>

<223> Sequence encoding rat HSP20

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gaattagcaa gtctatgtcc tgcagctata gcaccctact acctaaggc accatctgtc 180

gcgctcccaa ctgcccaagt gcccacggat ccaggctatt tcagcgttct gttagacgta 240

aagcatttta gtccagaaga aatttcagta aaagtagtgg gagaccatgt cgaggtacat 300

gctagacacg aagagagacc tgatgaacac ggtttcatcg ctcgagagtt tcaccggcgt 360

tatcgcttgc cgccggggt tgatcccgcg gccgtcacat cagcactcag tccggaggga 420

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gcaaaa 486

<210> 304

<211> 29

<212> PRT

<213> Artificial sequence

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<223> Synthetic peptide

<220>

<221> MISC_FEATURE

<222> (22)..(22)

<223> S is phosphorylated

<400> 304

Ala Gly Gly Gly Gly Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5 10 15

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu Lys
20 25

<210> 305

<211> 29

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<220>

<221> MISC_FEATURE

<222> (20)..(20)

<223> S is phosphorylated

<400> 305

Ala Gly Gly Gly Gly Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
1 5 10 15

Pro Arg Lys Ser Leu Trp Ala Leu Gly Arg Pro Leu Ala
20 25

<210> 306

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 306

Ala Gly Gly Gly Gly Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
1   5   10   15

<210> 307

<211> 26

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<220>

<221> MISC_FEATURE

<222> (19)..(19)

<223> S is phosphorylated

<400> 307

Ala Tyr Ala Arg Arg Ala Ala Ala Arg Gln Ala Arg Ala Trp Leu Arg
1   5   10   15

Arg Ala Ser Ala Pro Leu Pro Gly Leu Lys
            20   25

<210> 308

<211> 26

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<220>

<221> MISC_FEATURE

<222> (17)..(17)

<223> S is phosphorylated

<400> 308

Ala Tyr Ala Arg Arg Ala Ala Ala Arg Gln Ala Arg Ala Pro Arg Lys
1 5 10 15

Ser Leu Trp Ala Leu Gly Arg Pro Leu Ala
20 25

<210> 309

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> S is phosphorylated

<400> 309

Arg Arg Arg Arg Arg Arg Ala Ser Ala Pro Leu Pro
1 5 10

<210> 310

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<220>

<221> MISC_FEATURE

<222> (10)..(10)

<223> S is phosphorylated

<400> 310

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1               5                   10
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<211> 3

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 311

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Leu Arg Arg
1
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<210> 312

<211> 3

<212> PRT

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<220>

<223> Synthetic peptide

<400> 312

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Gly Leu Ser
1
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<210> 313

<211> 3

<212> PRT

<213> Artificial sequence

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<223> Synthetic peptide

<400> 313

Gly Leu Thr
1

<210> 314

<211> 3

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 314

Gly Lys Ser
1

<210> 315

<211> 3

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 315

Gly Lys Thr
1

<210> 316

<211> 3

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<223> Synthetic peptide

<400> 316

Asp Leu Ser
1

<210> 317

<211> 3

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<213> Artificial sequence

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<223> Synthetic peptide

<400> 317

Asp Leu Thr
1

<210> 318

<211> 3

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 318

Asp Lys Ser
1

<210> 319

<211> 3

<212> PRT

<213> Artificial sequence

<220>

<223> Synthetic peptide

<400> 319

Asp Lys Thr
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<210> 320

<211> 480

<212> DNA

<213> Artificial sequence

<220>

<223> Sequence encoding human HSP20

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gaattagcag cactttgtcc gaccacactc gcgccctatt accttagagc gccgtctgta 180

gccttaccag tcgctcaggt accaactgac ccaggccact tctccgtttt attagacgtg 240

aaacacttta gcccagaaga gatagcagtc aaagttgtag gagagcatgt ggaagttcac 300

gcgagacatg aagagagacc agatgaacat ggtttcgtag cgagagaatt ccatcgacgg 360

tatcgtctgc cccaggagt cgatcctgca gctgtgacga gtgcattatc gcctgaggga 420

gtgctcagta tccaagcagc cccgcgtca gcccaagccc cgcctccggc tgctgccaag 480